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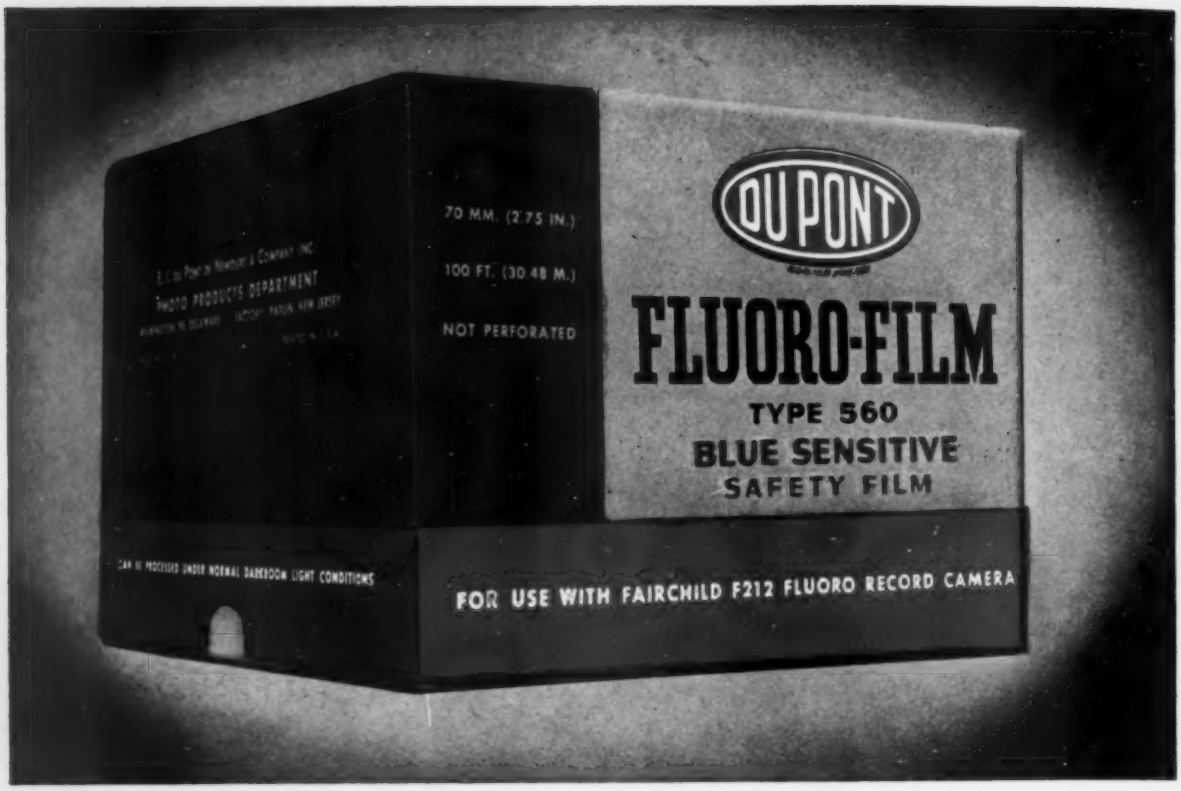

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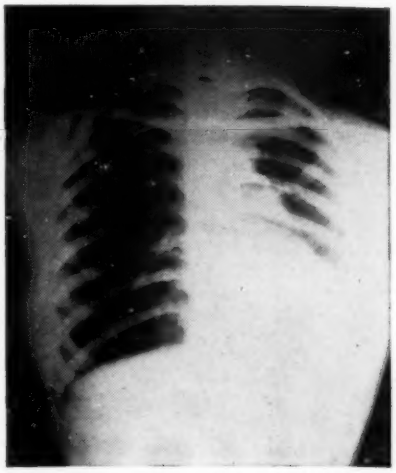

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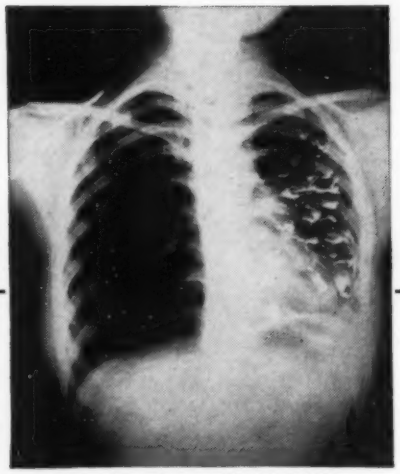

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SUPERFICIAL SPREADING CARCINOMA OF THE STOMACH

By ROSS GOLDEN, M.D., *and* ARTHUR PURDY STOUT, M.D.

NEW YORK, NEW YORK

CARCINOMA of the stomach is an epithelial growth which arises in the mucous membrane except in very rare instances where it may arise from ectopic epithelial cells in the deeper layers of the gastric wall.

To be detected by roentgen examination, a growth must produce alterations in the form or the movement of the stomach wall which can be recognized by this method of observation. If a cancer could grow without changing the gastric outline or movements, it obviously could not be detected. This has actually happened in some cancers of the fundus, where movements are rarely demonstrable.

After an abnormality has been detected, it must be differentiated from abnormalities produced by other conditions, particularly benign peptic ulcer and the inflammatory process ordinarily called gastritis.

The demonstrability of a carcinoma depends upon two factors: (1) the location in the stomach, and (2) the gross growth characteristics of the neoplasm.

In a group of 205 proved carcinomas seen at the Presbyterian Hospital, 75 per cent originated in the antrum, 20 per cent in the media and 5 per cent in the fundus. Fortunately, the great majority of carcinomas develop in the lower part of the stomach, which is accessible to the palpating hand, and where spontaneous movements occur normally. The importance of the location of the growth in the stomach is great but cannot be discussed further here.

The microscopic character of the cells composing a carcinoma of the stomach is of little or no significance as far as the problem of detection is concerned. On the other hand, the way the growth develops *grossly* is of great importance.

CLASSIFICATION

Malignant tumors have two basic growth characteristics, (1) the mass-producing quality, and (2) the invading or infiltrating quality. In some tumors one of these two qualities may predominate, almost to the exclusion of the other. Upon these physical growth characteristics Stout has based a classification of carcinomas of the stomach.

I. Fungating: grows into the lumen and produces a mass. It invades the deeper layers slowly and metastasizes late. It was found in 25 per cent of 200 cases.

* From the Departments of Radiology and Surgical Pathology, College of Physicians and Surgeons, Columbia University, and the Radiological Service of the Presbyterian Hospital, New York. Presented before the Forty-eight Annual Meeting, American Roentgen Ray Society, Atlantic City, N. J., Sept. 16–19, 1947.

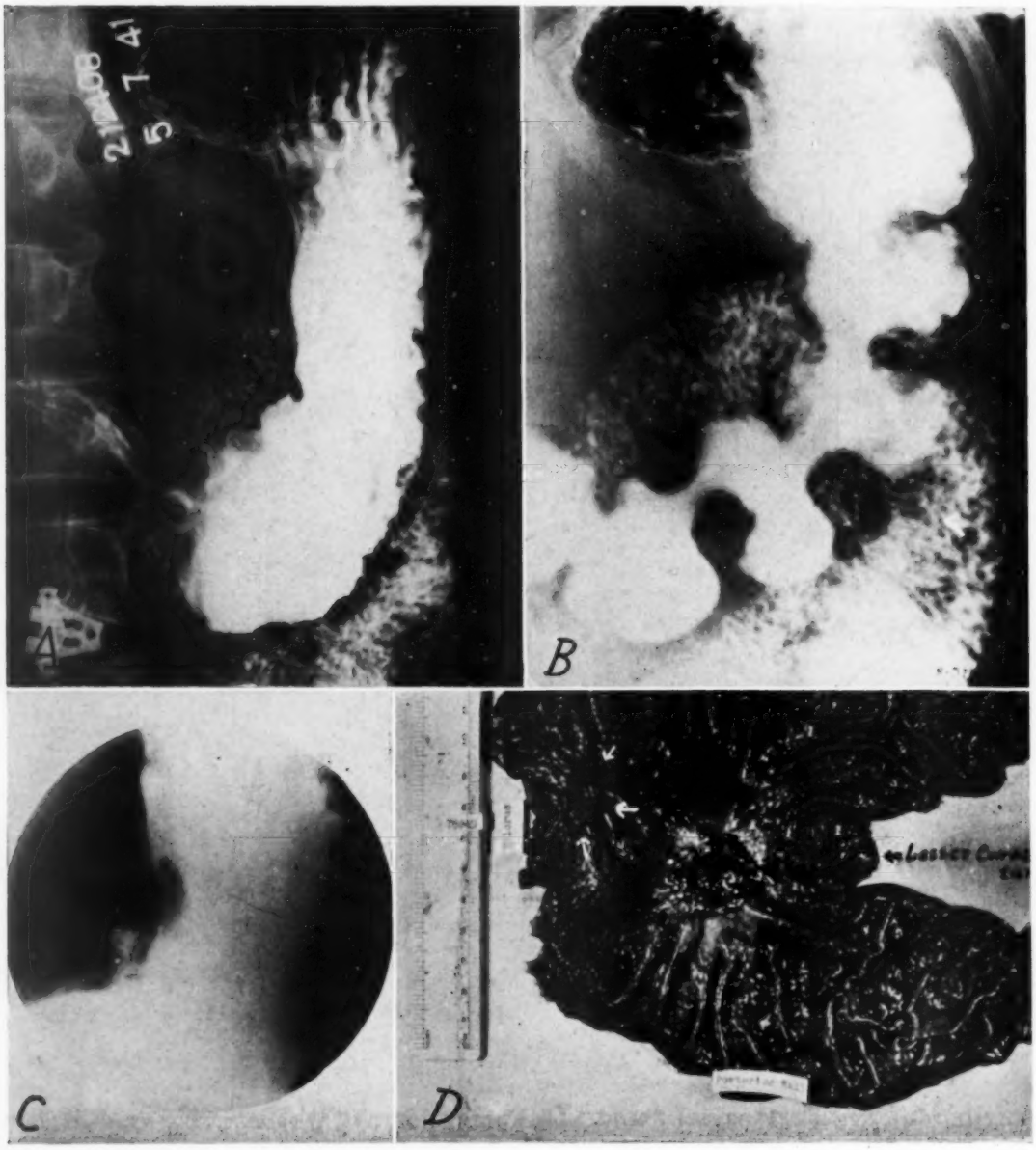

FIG. 1. Ulcerating Superficial Spreading Carcinoma of the Lesser Curvature and a Separate Superficial Spreading Carcinoma of the Anterior Wall of the Antrum.

A fifty-two year old man (Unit No. 640776) had pain beneath the lower end of the sternum for ten weeks, at first relieved by milk, Roentgen examination May 7, 1941 (*A*) disclosed a crater shadow in the region of the incisura angularis with a small six-hour gastric residue. Another examination June 10, 1941 showed the crater to be less angular and possibly slightly smaller. At gastroscopy May 21, 1941 the ulcer was seen but nothing consistent with carcinoma was detected. The second gastroscopy June 18, 1947 disclosed nodular swelling of the margin of the crater but the gastroscopist was not sure whether this was due to edema or malignant disease. At this time the patient was free from pain. At the third roentgen examination June 25, 1941 the crater shadow appeared to be about one-third its original size. During this examination the persistently sluggish stomach suddenly developed four peristaltic waves which were recorded with the spot film device (*B*). The site of the crater is indicated by the arrow. This gives the impression that the wall is perfectly flexible practically to the margin of the crater, and led one of us (R. G.) to believe that a diagnosis of carcinoma was not justified. However, all of these peristaltic impressions are unusual, if not abnormal, in that the greater curvature indentations are deeper than those on the lesser curvature and the

II. Spreading: grows along the wall and produces no mass.
   A. Superficial: spreads in the mucosa and submucosa. It was found in 14 per cent of 200 cases.
      1. Ulcerating—about 80 per cent.
      2. Non-ulcerating—about 20 per cent.
   B. Linitis Plastica type: spreads in the submucosa, muscle coat and subserosa. It was found in only 2.5 per cent of 200 cases.

III. Penetrating: grows through the wall to the serosa, and destroys and replaces the muscle. It was found in 26 per cent of 200 cases. It always ulcerates.

IV. Unclassifiable advanced growths found in 32.5 per cent of 200 cases.

This discussion is concerned with the superficial spreading type and the differential diagnostic problems connected with it.

PATHOLOGY

Superficial spreading carcinoma begins in and grows along the mucosa. The malignant growth replaces the mucous membrane, usually obliterates the mucosal folds and smooths out the surface. In the surrounding area the mucosal folds radiate toward the cancer, whether or not ulceration has occurred, and reach the edge of the involved area. In some places the tumor cells extend into the folds for a short distance and widen them. The malignant disease usually penetrates through the muscularis mucosae into the submucosa. In a few cases it is limited to the mucous membrane alone. In the most advanced cases, malignant cells penetrate between the muscle bundles of the tunica muscularis and may reach the serosa, but the muscle is not destroyed or replaced by the malignant tissue. This is in contrast to the penetrating type which does destroy and replace muscle.

Carcinoma of the stomach of any type is invariably associated with pathologic evidence of gastritis. In some cases this inflammatory process is far advanced.

MATERIAL

Superficial spreading carcinoma of the stomach was first recognized in the Department of Surgical Pathology of the Presbyterian Hospital in 1937. Between 1937 and 1947, 31 of them have been discovered.

The average length of time in 29 cases between the onset of symptoms referable to the stomach and the hospital admission during which operation was performed was nearly two years; the longest was ten years and the shortest was one month. In one case this figure could not be determined and in another the patient had not complained of digestive symptoms at the time of the examination. The latter was included in the

---

latter are quite wide with sloping margins. At the third gastroscopy July 2, 1941 the margins of the crater were elevated and nodular, the ulcer seemed to be healing poorly and the gastroscopist interpreted this as evidence of cancer. A pressure film (*C*) taken at the fourth roentgen examination (July 3, 1941) shows that the crater is smaller in depth but it is just as wide as ever at the level of the mucous membrane. This is in contrast to the way the ulcer healed in Figure 2. On the resected specimen (*D*) an ulcerating superficial spreading cancer 2.7 cm. in diameter was present on the posterior wall side of the lesser curvature about 5.5 cm. from the pylorus. A second and entirely separate superficial spreading carcinoma measuring about 1 cm. in diameter (approximately outlined by arrows) was present on the anterior wall very close to the pylorus which did not extend into the submucosa. On the proximal and posterior wall side of the ulcer, the mucosal folds come near the crater but do not enter it. On the inferior and anterior wall side they are interrupted at some distance from the crater. At the margins of the smaller cancer the mucosal folds are obliterated. Although the larger cancer measured on the specimen 2.7 cm. in diameter, in the living stomach it may well have had a greater diameter. Almost certainly the cancerous area was pulled inward by the contractions adjacent to the ulcer shown on (*B*). The question arises as to whether the abnormal width of the indentation on the lesser curvature and the greater depth of the indentation on the greater curvature can be taken as evidence of stiffening of the mucous membrane and submucosa by malignant cells, and as to the possibility that submucosal edema and inflammatory infiltration can produce a similar disorder of peristalsis.

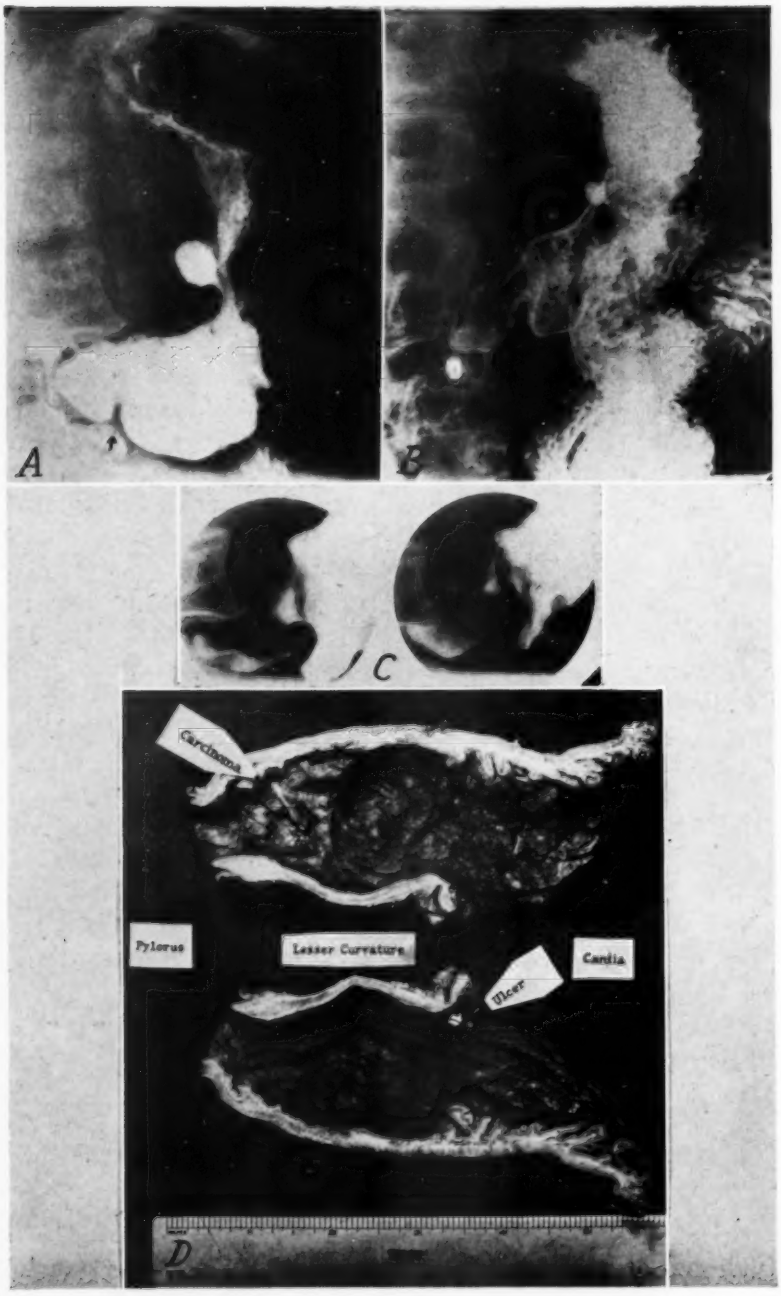

FIG. 2. Superficial Spreading Carcinoma of the Antrum with a Separate Healing Peptic Ulcer of the Lesser Curvature.

A fifty-two year old man (Unit No. 595656) complained of epigastric pain of two months' duration, accompanied frequently by vomiting. During this period he lost 17 pounds. Gastric analysis disclosed free HCl 65. Roentgen examination on December 14, 1939 (*A*) showed a large crater on the lesser curvature with undermined margins, an incisura on the greater curvature of the antrum thought to be due to reflex spasm, and a trace of six hour gastric residue. Gastroscopy December 29, 1939 disclosed a shallow ulcer on the anterior wall of the antrum, irregular in outline with slightly raised edges. Peristaltic waves faded out in the region of this ulcer. This was interpreted as ulcerating carcinoma. The patient refused operation. The second roentgen examination on January 4, 1940 (*B*) showed the crater on the lesser curvature to be smaller in depth and narrower at the level of the mucosa, which is characteristic of a healing peptic ulcer. The in-

series of 2,432 symptomless gastric survey cases reported by St. John, Swenson and Harvey.[1]

Of the 31 cases, 21 (67 per cent) were men, and 10 (33 per cent) were women. The age distribution was: under 40 years, 2; 41 to 50 years, 6; 51 to 60 years, 15; 61 to 70 years, 6; 71 to 80 years, 2. The oldest patient was 80 and the youngest 34 years.

One stomach contained two superficial spreading cancers (Fig. 1); the smaller was located on the anterior wall of the antrum and was about 1.0 cm. in diameter. This was the smallest in the series of 31 cases. The largest occupied an area of approximately 180 sq. cm.

In 2 cases, mixed types of carcinoma were present. One had a fungating growth, which had not penetrated through the muscularis mucosae, associated with a superficial spreading cancer which had penetrated into the submucosa at only one point. Another stomach showed superficial spreading cancer around a penetrating cancer. In 2 of the resected stomachs multiple foci of superficial spreading cancer were found with uninvolved mucous membrane between them.

Metastases to regional lymph nodes were present in only 15 of the 31 cases.

The superficial cancer developed in the lower half of the stomach in 30 of the 31 cases. In 1 case it occurred around the cardiac orifice and involved the fundus.

Peptic ulcer, as distinguished from superficial erosions of the mucosa, is defined pathologically as an excavation in the stomach wall which penetrates into and often through the muscle coat, sometimes into the gastrohepatic omentum. The destroyed muscle cannot be reproduced and the excavation, as it heals, must be filled in by scar tissue. The demonstration of localized scar tissue in the stomach wall establishes the fact that peptic ulcer is or has been present.

Cancer developed around an open peptic ulcer in 12 cases, in 3 of which secondary ulceration in the cancer occurred.

In 2 cases cancer developed in the mucous membrane over the scar of a healed peptic ulcer (Fig. 5).

The carcinoma itself ulcerated in 14 cases, in addition to the 3 ulcerating cancers associated with open peptic ulcers, mentioned above.

In 4 cases superficial spreading cancer was present without ulcer.

An open ulcer was present, therefore, in 26 (approximately 80 per cent) of 31 cases. One had a healed peptic ulcer with an ulcerating cancer in a different area. Another patient had ulcerating carcinoma of the anterior wall of the antrum which increased in size and a separate peptic ulcer high on the lesser curvature which diminished in size under observation (Fig. 2).

GASTROSCOPY

Gastroscopy was done in 11 cases. This procedure was carried out three times in 3 cases, twice in 2 cases, and once in 6 cases. In 9 of these 11 cases, the gastroscopist sooner or later found evidence interpreted as consistent with or suggestive of cancer. In 2 instances, he saw no evidence of carcinoma. The gastroscopist saw nothing to

[1] St. John, F. B., Swenson, P. C., and Harvey, H. D. An experiment in the early diagnosis of gastric carcinoma. *Ann. Surg.*, 1944, *119*, 225–231.

cisura in the antrum was reproduced. Pressure films of the antrum made four days later (*C*) showed an irregular barium shadow corresponding to the level of the anterior wall ulcer described by the gastroscopist. The second gastroscopy January 24, 1940 showed that the anterior wall ulcer had increased in size, and had a yellowish nodular base. The third roentgen examination January 25, 1940 disclosed marked spasm of the antrum, and still further decrease in the size of the lesser curvature ulcer. Partial gastrectomy was then done. The specimen (*D*, photographed after fixing) showed an ulcer on the anterior wall about 2.0 cm. in diameter and 0.1 cm. deep. Microscopic sections disclosed carcinoma limited to the mucosa and submucosa. One of 14 regional lymph nodes contained metastases. High on the lesser curvature was a healing benign peptic ulcer, which on the photograph appears as a hole in the stomach wall.

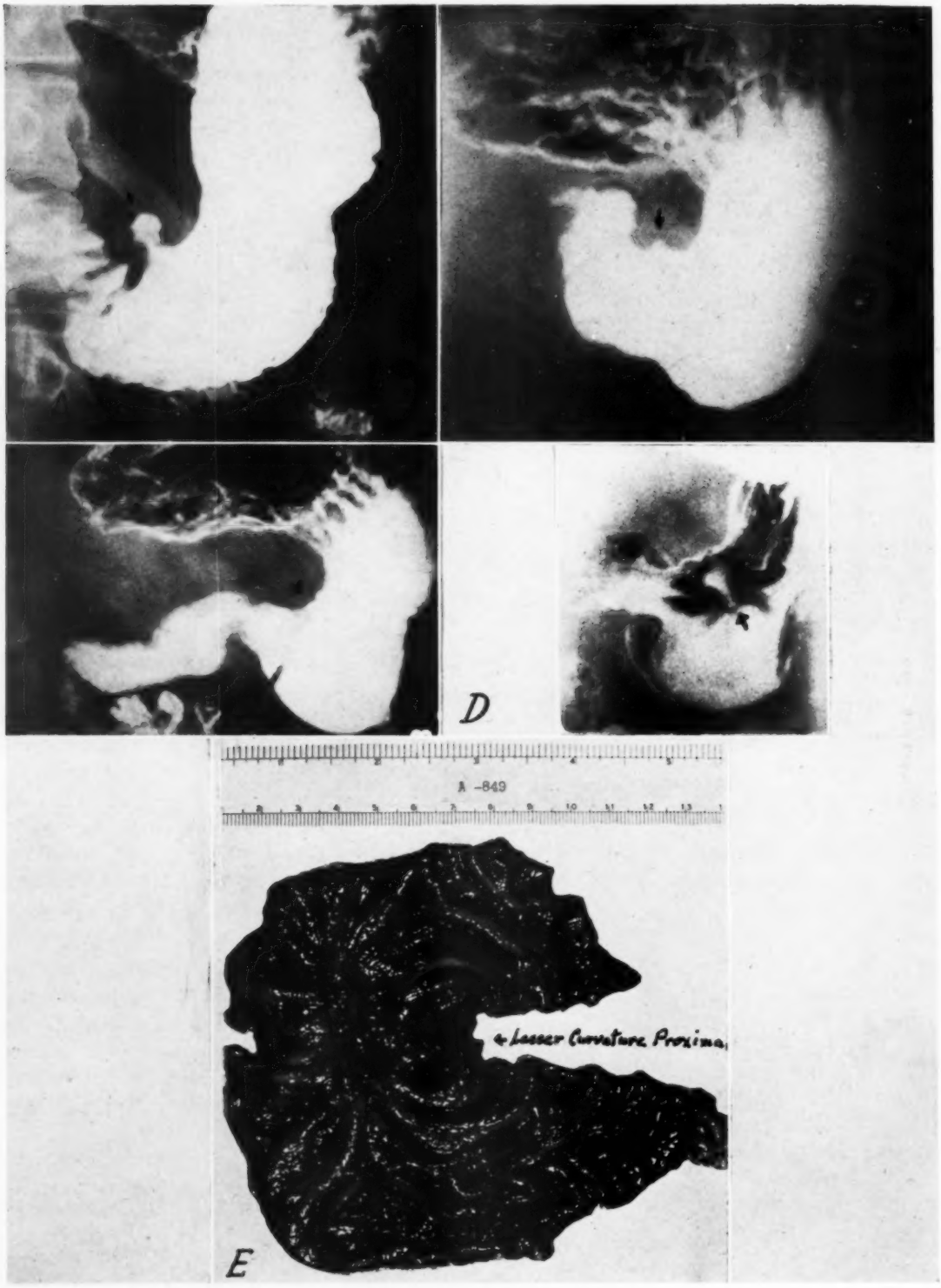

FIG. 3. Superficial Spreading Carcinoma Developing in the Margin of a Peptic Ulcer.

A fifty-three year old man (Unit No. 851031) was admitted December 4, 1946 because of epigastric pain which began four years previously. Roentgen examination in 1943 was said to have shown no ulcer. He was fairly comfortable on a strict diet for the next two years. The pain recurred and a roentgen examination

suggest cancer at the first observation in 4 cases, but on the second examination in 1 case and on the third examination in 3 cases, evidence of cancer was described. There is little doubt that cancer actually developed during the period of observation in at least 2 instances. In one of these approximately eleven months (Fig. 4), and in the other approximately five months elapsed between the gastroscopic examination at which no evidence of cancer was seen and the one at which evidence of cancer was detected. The involved area was visible at both examinations.

ROENTGEN EXAMINATION

An analysis of the records gives the following information about the results of roentgen examination of these stomachs. Two patients had examinations before admission, no details of which are available; on pathologic examination both of them had ulcerating cancers. Twenty-nine of the 31 patients had roentgen examinations at the Presbyterian Hospital, of which 24, on pathologic examination, had either ulcerating cancer or peptic ulcer with cancer. In 20 of these the ulcer was demonstrated by roentgen examination. The ulcer in the cancer was small and very superficial in a few, which is presumably the reason it was not demonstrated in the 4 cases. Certainly the presence of an ulcer helps in the detection of disease, particularly in the early cases.

The roentgen examination in 1 case disclosed what appeared to be a shallow ulcer on the lesser curvature. This crater shadow was smaller after three weeks of treatment. A diagnosis of carcinoma was made because of obliteration of mucosal folds around the crater shadow, with apparent loss of flexibility of walls. The pathologist found a shallow depression in the wall at the site of the growth but, because of the absence of necrosis, could not call the depression an ulcer.

Elongated spasm of the antrum, resembling the antral narrowing associated with antral gastritis (Fig. 4), was found in 9 of the 29 cases; a localized incisura at the level of the diseased area was present in 3 (Fig. 2).

A six hour observation was recorded in 26 of the 29 cases examined at the Presbyterian Hospital. A six hour barium residue was present in the stomach in 21 cases, of which 2 had twenty-four hour residues (Fig. 5). In 3 cases the stomach was empty at six hours. A six hour observation was apparently not made in 5 cases. It appears that delay in emptying the stomach occurred in some degree in approximately three-quarters of the cases, but is of no significance in the differential diagnosis.

The elapsed time between the first roentgen examination and the operation in the first 7 cases which were seen in 1937–1938 inclusive averaged 115 days; the longest was 191 days and the shortest

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elsewhere on May 29, 1945 disclosed a penetrating ulcer of the lesser curvature of the antrum with undermined margins (*A*). On a dietary regimen he had no symptoms for over a year when they recurred. A roentgen examination elsewhere in November, 1946 disclosed a crater shadow on the lesser curvature of the antrum (*B*) which is not as deep as the crater shown in 1945. Another roentgen examination at the Presbyterian Hospital December 26, 1946 disclosed a peculiar double crater on the lesser curvature (*C*). A spot film without pressure taken with the patient supine (*D*) shows the crater *en face*. The crater has a peculiar trilobed appearance. The mucosal folds do not run into the crater on the lesser curvature and the pyloric side. At operation the surgeon found evidence of an ulcer with nothing he could consider suggestive of a carcinoma. The resected specimen (*E*) showed an ulcer on the lesser curvature which seemed to be made up of three confluent craters, the largest of which had a punched out appearance with overhanging edges on the proximal side. The three confluent craters occupied an area of about 3 cm. along their widest diameter. The two smaller craters were shallow and upon microscopic examination were found to be ulcers in superficial spreading carcinoma which arose on the lesser curvature and pyloric side of the peptic ulcer. The arrow points to the largest ulcerated area in the cancer. The secondary ulceration in the cancer explains why the crater, as seen *en face*, had a trilobed appearance. This patient undoubtedly had at least one peptic ulcer which healed. The recurrence in 1946 developed cancer on part of its margin before it had time to heal.

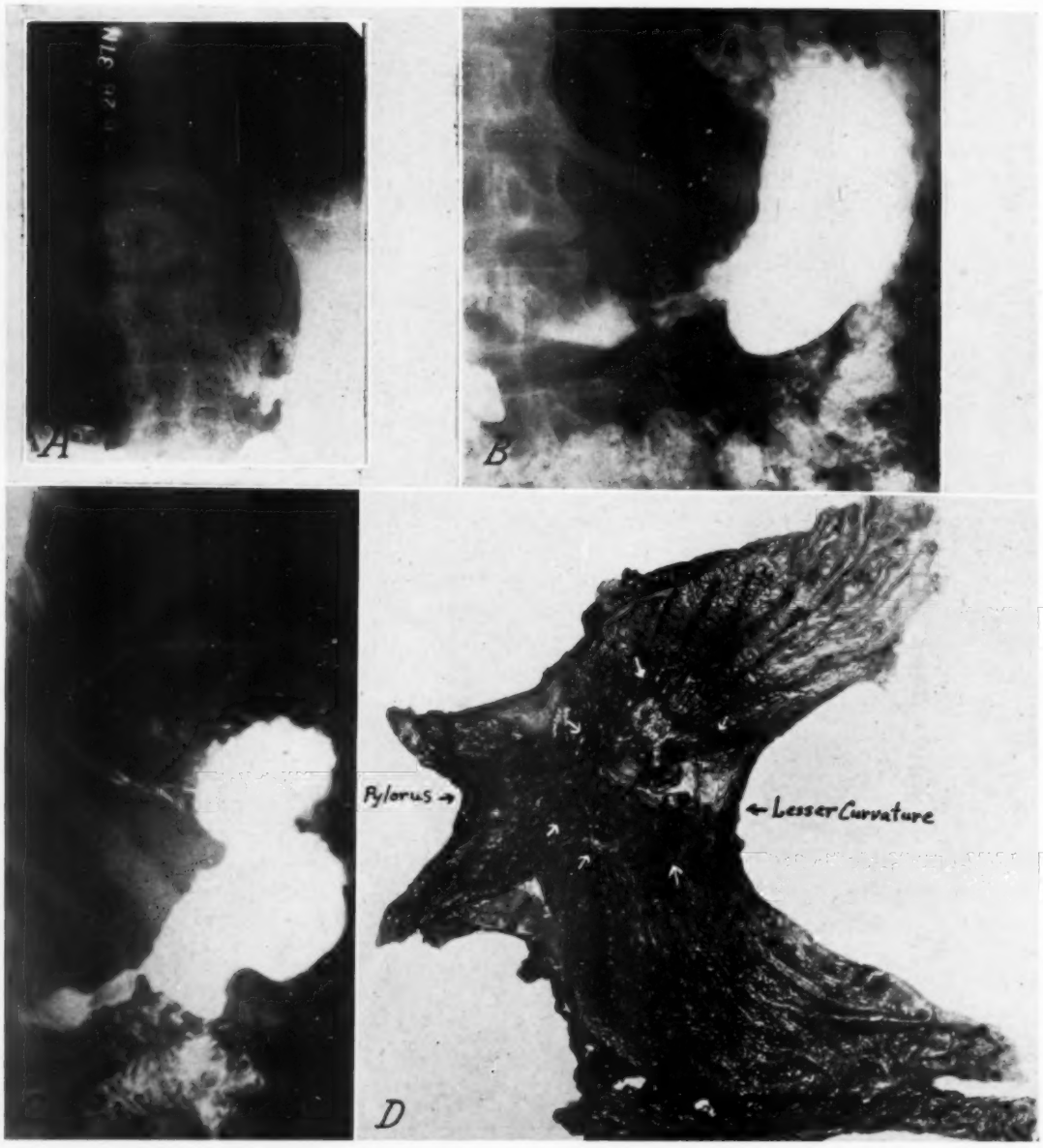

FIG. 4. Superficial Spreading Carcinoma of the Lesser Curvature with Involvement of the Mucosa Alone and Associated with Antral Spasm.

A fifty year old man (Unit No. 522052) complained of gas after meals for four years and of stabbing epigastric pain relieved by milk for one year. Roentgen examination June 28, 1937 (*A*) disclosed spasm of the prepyloric region interpreted as antral gastritis. Gastroscopy July 14, 1937 disclosed erosions on the anterior wall of the stomach in the antral region, each about 6 to 7 mm. in diameter. The second gastroscopy, December 1, 1937, showed atrophic mucosa where the erosions had previously been seen. The second roentgen examination October 4, 1938 (*B*) showed a striking increase in the degree and in the length of the spasm of the antrum. The third gastroscopy November 7, 1938, approximately eleven months after the second, disclosed small nodules on the mucous membrane along the lesser curvature and anterior wall of the antrum, interpreted as diffuse carcinoma. No peristaltic movement was seen in this area. The cancer developed where the erosions were seen at the first gastroscopy and the atrophic mucous membrane at the second. The third roentgen examination on November 14, 1938 (*C*) showed spasm of the antrum with small irregularities on the lesser curvature above the narrow region. On the greater curvature opposite these irregularities is a peristaltic indentation with no corresponding indentation on the lesser curvature. Just proximal to the irregular area on the lesser curvature is a peristaltic wave with indentations on both curva-

thirteen days. The patient who was operated on thirteen days after the first roentgen examination was the last one of the 7 seen in 1937–1938. The average time for the first 6 cases in this group was considerably longer than 115 days.

The average elapsed time between the first roentgen examination and the operation in 13 cases seen between 1939 and 1942 inclusive was twenty-six days; the longest was fifty-three days and the shortest was three days.

The average elapsed time between the first reontgen examination and the operation in 9 cases seen in 1943 to 1947 inclusive was thirty-eight days; the longest was 142 days and the shortest was five days. The patient with the longest time in this group was a woman, aged seventy, with hypertension and other complications. In spite of a positive diagnosis of cancer of the stomach by roentgen examination on admission and a similar diagnosis made by gastroscopy about three months after admission, the surgeons hesitated to operate upon her. Her complicating conditions made operation more than usually hazardous. Although she had postoperative lobular pneumonia, the fatal outcome was apparently precipitated nine days after the operation by a severe reaction following the intravenous administration of an amino acid preparation. However, the delay between the diagnosis by roentgen examination and the operation is now recognized as a mistake. Without this one case the average time between the first roentgen examination and operation in this last group would have been about the same as that of the second group.

Two patients were examined elsewhere and the dates are not recorded.

The roentgen examinations in these cases were done by a number of individuals who varied greatly in experience. Some of them were residents in training. However, the interpretation of the roentgen examination was at times very difficult even for the most experienced observers. The analysis of the elapsed time given above shows, nevertheless, evidence of improvement in the ability of the observers of these cases, both radiological and clinical, to reach a decision to operate.

PROBLEMS IN DIAGNOSIS

In retrospect, the difficulty in the diagnosis of superficial spreading carcinoma of the stomach lies mainly in three problems. The first problem is the detection of cancer developing around an open peptic ulcer. The second problem is the detection of cancer developing in association with spasm of the antrum. In a few cases these two problems were combined. The third problem is the possible effect of cancer growing in the mucosa alone or in the mucosa and submucosa on peristaltic movements and the flexibility of the wall.

1. Can cancer developing around the margins of an open peptic ulcer be detected?

If secondary ulceration in the cancer occurs, it may produce apparent lobulation

tures. The resected specimen (*D;* unfortunately not photographed until after fixing) disclosed an irregular lesion about 6×9 cm. on the lesser curvature and extending onto both anterior and posterior walls, approximately outlined by arrows. In its center were small nodules 3–5 mm. in diameter with slightly depressed areas of ulceration. The involved area of mucosa was immovable over the muscle. Microscopic examination showed carcinoma involving only the mucosa, associated with chronic gastritis. No evidence of metastases was present in the regional lymph nodes. It seems reasonably certain that carcinoma developed in the atrophic mucosa some time in the eleven months between the second and the third gastroscopy. The significant roentgen manifestations were (1) an increase in the spasm of the antrum, (2) the small irregularities on the lesser curvature, and (3) the obliteration of peristalsis along the involved area of the lesser curvature. Although the cancer involved only the mucosa, the mucous membrane was immovable over the muscle coat. This fixation of mucosa to muscle cannot be attributed to the cancer which had not extended into the submucosa. Presumably, therefore, it must be the result of an inflammatory reaction in the submucosa associated with gastritis. It is uncertain whether the obliteration of peristalsis on the lesser curvature was due to the carcinoma in the mucous membrane or to the submucosal inflammatory reaction, or to a combination of the two.

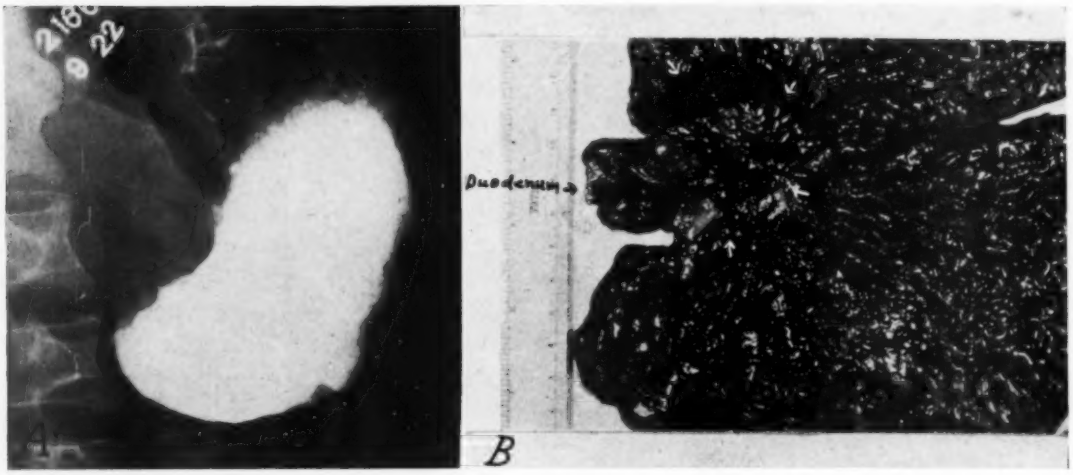

FIG. 5. Superficial Spreading Carcinoma Arising over the Scar of a Healed Peptic Ulcer, Associated with Prepyloric Spasm.

A fifty-six year old man (Unit No. 650712) had epigastric fullness and vomiting about a quarter of an hour after eating for two years, increasing in severity. He had no pain. He lost 23 pounds in six months. Roentgen examination on August 26, 1941 showed that no barium left the stomach in six hours, and that a large twenty-four hour gastric residue was present. The cause of the retention, aside from spasm, could not be determined. He was given dietary treatment with daily gastric lavages. The second roentgen examination September 5, 1941 showed no evidence of improvement in the emptying of the stomach. At operation on September 11 a puckered scar was found on the lesser curvature in the prepyloric area. A posterior gastroenterostomy was done. The third roentgen examination September 22, 1941 (*A*) disclosed evidence of a complete pyloric obstruction. Very little barium passed through the gastroenterostomy. At the second operation, September 25, 1941, edema of the stoma was found. Partial gastric resection was done. The specimen (*B*) showed organic stenosis of the pylorus which was so narrow that a probe was passed with difficulty. The pyloric muscle was hypertrophied. In the prepyloric region the mucosa was thin and was fixed to the muscle coat. The 1.5 cm. scar of a healed ulcer was present on the anterior wall side of the lesser curvature about 3 mm. from the pylorus. On microscopic examination a carcinoma 6 cm. in diameter was found in the mucosa over the scar, which had penetrated slightly into the cicatrix at one point. The approximate area is outlined by arrows. The mucosa was not thickened and the cancer was not recognized by the pathologist on inspection and palpation of the fresh specimen. The patient died at home five and a half years later with a mass in the right upper quadrant presumably from metastases.

of the margin of the crater shadow. To demonstrate this, films of the crater filled with barium should be made in some way so that the form of the crater's rim can be seen *en face* as well as in profile (Fig. 3). In peptic ulcer, the mucosal folds run into the crater. If cancer develops around the ulcer, the mucosal folds stop at the edge of the cancer. The failure of peristaltic indentations to run up close to the crater is suggestive but not conclusive evidence of cancer. This may be difficult to demonstrate with certainty, because of the disorder of peristalsis so frequently associated with gastritis and antral spasm. Under treatment, the healing crater of the peptic ulcer should diminish in size in all directions, in transverse diameter across the mucosal margin as well as in depth; whereas the cancerous crater may diminish in depth but diminishes little or not at all in transverse diameter (compare Figures 1 and 2).

2. Does cancer in the mucous membrane and submucosa cause spasm of the muscle coat, or is the spasm the result of an inflammatory process in the stomach wall?

A study of our cases suggests that cancer under these conditions can cause spasm of the muscle, but it usually is no different from the spasm often associated with inflammatory disease of the wall. Unfortunately, edema and other inflammatory changes are often present with carcinoma. If the spasm increases either in degree or in

length while the patient is under observation, carcinoma should be suspected. A localized incisura on the greater curvature, which may vary in width from time to time, has been present in some cases, and should serve to direct critical attention to the wall at that level.

3. Does cancer in the mucous membrane and submucosa modify peristaltic movements and stiffen the wall in such a way that it can be differentiated from the effect of inflammation?

Almost certainly this differentiation cannot be made in all cases at the present time. Probably the effect would depend upon the degree of inflammation and of submucosal edema. Carcinoma infiltrating the mucous membrane has definitely obliterated peristalsis over the infiltrated area in some cases (Fig. 4) and apparently not in others. The wave may be shallow in the infiltrated area and normally deep opposite it (Fig. 1). It seems possible that the degree of interference with the movement of the gastric wall depends upon the size of the area involved by the carcinoma. One difficulty is to be sure of the accuracy of the observation. It seems advisable to assume that carcinoma is probably present if dampening or obliteration of the peristaltic impression occurs over a localized area, particularly if small irregularities of the margin or other suggestive signs are present.

SUMMARY AND CONCLUSIONS

Superficial spreading carcinoma of the stomach grows along the mucosa or in the mucosa and submucosa. Its physical effects on the stomach wall are: (1) replacement of the mucosa; (2) radiation of the mucosal folds toward the growth; (3) obliteration of the folds by the growth; (4) widening and stiffening of the folds immediately around the growth; (5) nodule formation on the surface; (6) ulceration. This type of cancer does not produce a mass.

A study of 31 cases has shown that the difficulty in the great majority was not to detect an abnormality on roentgen examination of the stomach but was rather to make sure that cancer was or was not present in an obviously abnormal stomach. Cancer may develop at any time in a patient who has suffered for years from peptic ulcer or gastritis. To detect these cancers, the examination must be elaborate and painstaking, with fluoroscopy and films in various positions. Roentgen cinematography would be very helpful, if it could be switched on at the time a rare peristaltic movement occurs in a persistently sluggish stomach. We must look for and try to understand details of structure and movement of the stomach wall to which we have paid too little attention, e.g., the character and shape of the margins of the stomach shadow, the shape of the ulcer crater, the relation of the mucosal folds to the crater. The crater, if possible, should be seen *en face* as well as in profile. Lobulation of the margins of the crater, a persistent incisura in the antrum even in the absence of a demonstrable ulcer, an increase in the length and degree of spasm of the antrum, and a diminution in the depth but not in the transverse diameter of the mucosal margin of a crater are signs suggesting cancer.

This study has emphasized to us the difficulty of determining accurately what area on the resected specimen corresponds to a given point on the shadow of the living stomach, unless a gross lesion such as an ulcer is present. Even then it is difficult to estimate on the film the extent of the involved area as shown on the specimen. With resection, the stomach muscle contracts but how much it contracts is not known. Nevertheless we must determine the exact extent and character of the disease in the wall of the resected specimen and correlate it as best we can with the roentgenologic examination. In no other way can knowledge concerning small early cancers of the stomach be increased.

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PENETRATING WOUNDS OF THE ABDOMEN

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INTRODUCTION

IT IS of prime importance to determine whether a penetrating missile has or has not entered the peritoneal cavity. Often, physical signs and symptoms are sufficient to warrant a laparotomy. However, more often than it is generally believed, the signs and symptoms are misleading. Thus, nearly all penetrating wounds of the retroperitoneal space and of the abdominal wall itself produce signs and symptoms which are, for practical purposes, indistinguishable from those accompanying intraperitoneal injuries. Penetrating wounds of the lower chest are also capable of producing pain and rigidity of the abdomen as well as the shock picture. Conversely, many cases of definite intraperitoneal injuries have been encountered with few or no signs and symptoms. This has happened a sufficient number of times to make the initiated and the experienced surgeon rely greatly on any roentgen finding which indicates with certainty that a missile has entered the peritoneal cavity.

These general statements have been attested to by many authors. Reinberg,[6] in a review of roentgen diagnosis in gunshot wounds in U.S.S.R., states that in many cases of peritoneal entrance symptoms were so few that surgeons would not consider laparotomy until roentgen diagnosis urged it. Lenk,[2] in a review of the role of the roentgen ray in World War I, states the same.

This study is based on over 600 abdominal roentgen examinations made in World War II in an evacuation hospital close to the front lines, in which the examination was made within hours of the time of the injury. Particular stress will be laid on a new aspect of the technique of such an examination.

THEORETICAL CONSIDERATIONS

When a missile enters and leaves the abdomen, an anteroposterior and a lateral view are obviously of no value to determine whether the missile has or has not entered the peritoneal cavity. When a missile enters and does not leave the abdomen, it is presumed that an anteroposterior and a lateral view will aid in solving this perplexing and important problem. Experience in many cases, however, shows that this examination is of little value and often misleading for a number of reasons. The final resting place of a missile gives no indication of its course through the abdomen. Thus, we have seen cases in which a missile enters the anterior abdominal wall from the side and lodges in the anterior abdominal wall in the midline, and in its course enters the peritoneal cavity. On the other hand, we have seen a bullet enter the left posterior abdominal wall, course through the abdominal wall on the left side, and lodge in the anterior abdominal wall in the midline without traversing the peritoneal cavity. In these cases, an anteroposterior and lateral view can be definitely misleading. Thus, in the first instance, the point of entrance of the missile, and the anteroposterior and lateral views might lead to the conclusion that the peritoneum was not entered, and in the second instance, lead to the conclusion that the peritoneum was entered. An anteroposterior and lateral view can also be misleading because, when the missile is far from the film, the slightest shift of the patient away from the perpendicular in the lateral exposure can make a great error in the determination of the final position of the missile on the roentgenogram. In severely injured patients it is often impossible, because of associated injuries, to position the patient in a perfect lateral. Then, too, we have seen cases in which a missile lodged in a large retroperitoneal hemorrhage and protruded so far into the abdomen that on the anteroposterior and lateral views the location of the

missile appeared to be in the exact center of the abdominal cavity.

The most reliable roentgenological index of the course of a penetrating wound is a demonstration of a pneumoperitoneum. Roentgen visualization of spontaneous pneumoperitoneum and its diagnostic significance has received a great deal of attention in medical literature. M. Weinberger,[12] in 1908, and Popper[5] in 1915, were among the first to report on subphrenic air. Nearly all the reports deal with subphrenic air and its significance in the diagnosis of ruptured peptic ulcer. Thus, Vaughan and Brams[9] showed the presence of air in 86.7 per cent of 65 cases of ruptured peptic ulcer; Vaughan and Singer[10] showed it in 85.7 per cent of 63 cases; Odom and DeBakey[3] in 64.6 per cent of 164 cases. DeBakey,[1] in a review of the literature of 1,267 cases, states that this finding is present in 69.4 per cent. Pearce[4] believes that the figure is closer to 50 per cent. Although it has been known for some time that the appearance of a pneumoperitoneum is of diagnostic significance after a traumatic wound of the abdomen, only a few reports of a series of such cases have appeared in the literature. Reinberg[6] writes of the importance of this examination to the military surgeon of U.S.S.R. in World War II. Lenk[2] in 1916 reported on this finding after his experience in World War I.

Authors who have written about the demonstration of pneumoperitoneum state that the patient should preferably be examined in the sitting position so that the air may rise to the diaphragm and above the liver and stomach. If this position is impossible, then it is advised that the patient be placed on his left side and a postero-anterior or anteroposterior exposure made with a horizontal beam of roentgen rays. This demonstrates free air under the right diaphragm. If this position is impossible, then it is suggested that the patient be examined in the recumbent position with a horizontal beam of roentgen rays. This order of preference is generally accepted, and few authors bother to speak of the recumbent position at all. It is the purpose of this paper to show that the recumbent position is the preferable one in the demonstration of free air in the peritoneal cavity.

THESIS

With the above information as a guide, we examined our abdominal injury cases in the conventional sitting, or left lateral positions. However, so many war casualties have multiple injuries that it is difficult, wrong, and in many cases impossible to position the patient. As a result, we were forced to examine the patient in the position that the patient came to us—usually in the supine position. A 14 by 17 inch cassette was held erect by a litter-bearer on either side of the patient, and a lateral exposure made with the central ray directed horizontally about 2 inches posterior to the anterior abdominal wall. After we learned to detect free air in the peritoneal cavity in this view, we were greatly surprised to find that our correlation with the clinical and surgical findings was much higher than in those cases where the more usual sitting and left lateral positions were taken. A possible explanation presented itself and was later proved in at least 10 cases. When a patient with an intraperitoneal injury arrived in the roentgen-ray tent in the supine position, the free air presumably rose to the top and was concentrated in the peritoneal cavity in close apposition to the anterior abdominal wall. When the patient's position was changed for the few seconds of a roentgen examination, it was presumed that not enough time elapsed for a small amount of air to collect in the new position to be visible on the roentgenogram. Thus, Thaxter,[8] in showing that no harm is done to the patient in placing him in a sitting position, states that this position should be held for only fifteen seconds. Figure 1 is the roentgenogram of a soldier whose original film taken in the sitting position failed to show air. Because this patient was so definitely positive clinically, and because of the above theoretical considerations, we roentgenographed him again after an interval of thirty minutes, in the supine position, with this gratifying result (Fig.

FIG. 1. The original sitting film of this patient showed no free air. Repeat examination in the supine position shows free air. Note that the free air follows the curve of the diaphragm, is sharply demarcated anteriorly and posteriorly, and is limited above and below by tapering points. Note on the same film a large gas bubble with a fluid level in the lower abdominal region. This was interpreted as a ruptured bladder and later confirmed on operation.

3). Convinced of its superiority, this method of examination became our routine. However, we had many combined abdominal and chest injuries, and since our surgeons requested erect chests, we had the opportunity to see at least 10 cases in which we were able to demonstrate free air in the supine view of the abdominal examination, and not in the erect position of the chest examination. The reverse was never found, although many roentgenograms showed air in both views. Figures 2 and 3 are of the same patient and demonstrate that roughly twice as much air is seen in the supine as in the erect film.

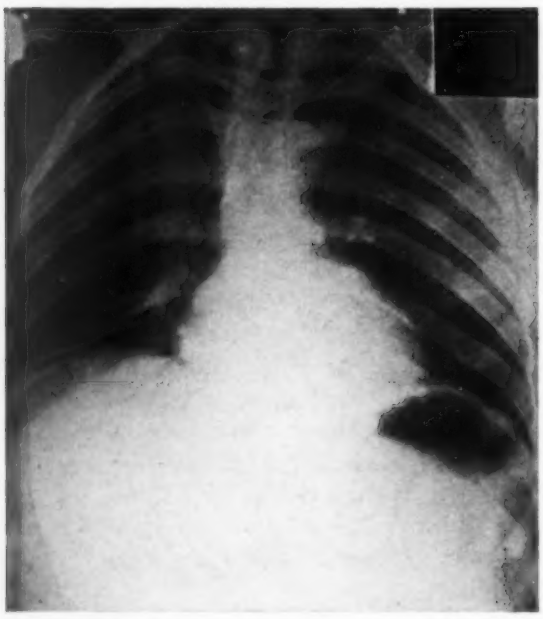

FIG. 2. Erect film showing free air under the right diaphragm.

After our technique was perfected, we found a very high correlation in over 600 examinations. Air was found in about half of these and, in all but 2 there was surgical confirmation of intraperitoneal injury. These 2 cases were very similar in that both had extraperitoneal rupture of the rectum and retroperitoneal hemorrhage, and since a colostomy was indicated, fortunately no harm was done by the laparotomy which we urged. A possible explanation for this "false" finding is the failure of the surgeons to demonstrate a small opening in the peritoneum through which air entered from the outside. Small peritoneal tears are extremely difficult to find in the pres-

ence of retroperitoneal hemorrhage. We have seen several cases of intestinal perforation or intraperitoneal hemorrhage in which a peritoneal tear could not be demonstrated at operation. Thus, it is probable that these 2 "false" positives were not false at all, and our correlation was practically 100 per cent. In many cases the was so high that many clinically doubtful cases were spared a laparotomy because of the absence of a pneumoperitoneum.

SIGNIFICANCE OF PNEUMOPERITONEUM

Most authors feel that free air in the peritoneal cavity is the result of the escape of air from the intestines. Reinberg[6] states

Fig. 3. The same patient taken in the recumbent position. This demonstrates that about twice as much air is seen in the recumbent view as in the conventional erect view. Note again tapering points which differentiate free air from air in bowel loops.

demonstration of free air was the deciding factor, and in a few, the only indication for a laparotomy.

Less than 10 per cent of those cases in which free air was not demonstrable were operated upon because the clinical findings urged laparotomy. This was especially so in old cases in which peritonitis was already present. It is entirely possible that the small amount of air had been reabsorbed in the few days since the original trauma. However, we had some early clinically positive cases which failed to show air, and for which there was no satisfactory explanation. The capacity of our roentgen-ray apparatus was only 15 ma. and it is possible that with better equipment, permitting faster exposure, this error might be lowered. However, even this correlation

that it has not yet been settled that air can enter the peritoneal cavity with a missile. In our experience, it is undoubtedly true that air does enter with the missile.

The peritoneal cavity is a potential or capillary space between the visceral and parietal surfaces, and it has been experimentally shown by Wagoner[11] in 1926 and confirmed by Salkin[7] in 1934 that the intra-abdominal pressure is 50 mm. of water less than atmospheric pressure. Wagoner[11] states that the observant surgeon notices the inrush of air when the peritoneum is entered. Thus, from theoretical considerations alone, one can expect air to enter the peritoneal cavity when the peritoneum is perforated. Free air in the peritoneal cavity following a penetrating wound simply means that the peritoneum has been en-

FIG. 4. Free air in a case in which no hollow viscus was perforated. The air entered through a ruptured diaphragm following a chest injury. In general, these cases show the most free air.

tered, and not necessarily that there has been visceral involvement. We have conclusive and presumptive evidence that this is true. We have seen at least 6 cases of demonstrable pneumoperitoneum in which a missile entered the peritoneum, made one or more perforations of the mesentery, and did no other damage. We have seen many cases of demonstrable pneumoperitoneum in which a missile entered the peritoneum, lodged in the liver and did no other damage. These instances furnish conclusive proof that the pneumoperitoneum was produced by air introduced from the outside.

FIG. 5. This shows a large amount of air in which no hollow viscus or diaphragm was ruptured. The air was introduced from the outside.

Presumptive evidence that the free air is mostly externally introduced is obtained from several facts. There is no correlation between the amount of visible air, or the number of perforations, or the type of hollow viscus perforated. Thus, Figure 4, showing a large amount of air, is a case in which no hollow viscus was perforated, and the air came from the lung through a ruptured diaphragm. In general these cases show the most air. Figure 5 is a case in which the peritoneum was entered without visceral or diaphragmatic damage. Figure 6 shows a small amount of air in which the stomach had two perforations. The anteroposterior view taken at the same time showed a large gastric dilatation which is evident on this film. We have seen a few cases of gastric dilatation with perforation in which no free air could be demonstrated. These same considerations are true for dilated perforated colons. Apparently the elasticity of the gastrointestinal wall can immediately seal a small perforation, and this probably accounts for our relatively symptom-free cases.

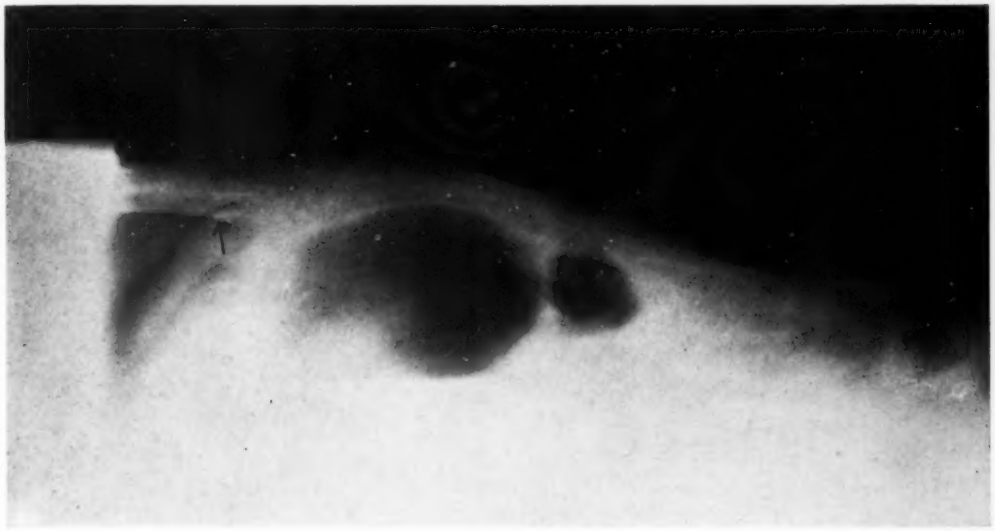

Fig. 6. This is a case in which operation disclosed two perforations in the stomach. Although a large gastric dilatation is present, nevertheless only a small amount of free air is visible. Figures 4, 5 and 6 demonstrate that there is no correlation between the amount of free air and the presence or absence of hollow viscus perforations.

Undoubtedly, some of the free air we see is partially intra-intestinal in origin, but the evidence shows that we may say with absolute certainty only that the peritoneum has been entered. This being so, is a laparotomy indicated in the presence of a pneumoperitoneum? The rarity of such an occurrence without serious visceral damage makes it imperative to explore. Then, too, it is felt that the introduction of antibacteriological agents and repair of the peritoneal wound is good prophylactic treatment. Most of our relatively symptom-free cases were those of peritoneal entrance in which only the liver was injured. The surgeons were tempted not to operate in these cases, but the few symptom-free cases with many intestinal perforations persuaded them to operate. Since it is felt by many that liver cases should be drained, this is an additional reason for a laparotomy and exploration.

TECHNIQUE

The patient is examined in the position in which he arrives in the roentgen department. Usually, this is supine, but we have had a few cases that came to us lying on

FIG. 7. In the Fowler position the free air can be confused with air in the costophrenic sulcus.

one side, and some in the prone position. When the patient is supine, a 14 by 17 inch cassette is held vertically on either side of the patient, and a lateral exposure is made with the central ray directed about 2 inches posterior to the anterior abdominal wall at the diaphragm level. The target film distance is 40 inches, and since grid lines of a stationary grid interfere greatly with interpretation, a small cone is used instead. Whether a Potter-Bucky diaphragm will improve the technique is problematical. A more rapid time than we have been forced to use will undoubtedly improve results. The patient is placed in a slight Fowler position in order to concentrate the free air in a small area posterior to and below the diaphragm.

DIFFERENTIAL DIAGNOSIS

The lateral roentgenogram with the patient in the supine position has not been

FIG. 8. The same case as Figure 7 in the Trendelenburg position demonstrates movability of the free air.

the preferred one, because it is felt that the identification of free air in this position is difficult. This is probably so only because there has been so little experience with this type of roentgenogram. The diagnosis is relatively easy, and extremely small amounts of free air can be positively identified. Free air in the peritoneal cavity must be differentiated chiefly from fat, air in the intestines, and air in the soft tissues. It is differentiated from air in the soft tissues by its very distinct location—it is posterior to the muscle layer of the anterior abdominal wall, and when it is concentrated cephalad by the Fowler position, it is posterior to and below the diaphragm, and follows the curve of the diaphragm. It is sharply demarcated anteriorly by the parietal peritoneum and posteriorly by the abdominal viscera. This sharp demarcation anteriorly and posteriorly is of great importance in that it readily distinguishes free air from peritoneal fat which is not sharply demarcated and fades gradually into the surrounding tissues. In addition, fat is denser than air and usually does not appear quite as black. Free air is readily differentiated from air in loops of bowel. In the latter, the air is enclosed in a limiting membrane and its upper and lower borders are consequently rounded. Free air in the peritoneal cavity characteristically terminates in tapering points. This, too, helps to differentiate free air from peritoneal fat. Occasionally, other shadows appear and may be confusing. A rib may cross the diaphragm in such a way as to produce a confusing black line. Occasionally, it is difficult to distinguish a small triangular collection of free air from the similarly shaped extremity of the anterior costophrenic sulcus. When in doubt, films taken in the Trendelenburg as well as the Fowler position show free air changing its position in contrast to fat or bowel loops which remain relatively stationary (Fig. 7 and 8).

SUMMARY AND CONCLUSIONS

1. Anteroposterior and lateral views are of little value in determining whether a missile has or has not penetrated the peritoneal cavity.

2. Clinical symptoms and physical findings are sometimes misleading. The best roentgenological index is the presence of a pneumoperitoneum.

3. A pneumoperitoneum indicates only that the peritoneum has been entered. It does not necessarily mean visceral involvement although a laparotomy is indicated.

4. Nearly 100 per cent of all cases which show pneumoperitoneum have had peritoneal entrance. Therefore, pneumoperitoneum is a positive indication for a laparotomy.

5. In those cases in which a pneumoperitoneum could not be demonstrated, less than 10 per cent were surgically positive. This error can probably be reduced with better equipment. Nevertheless the error is sufficiently small so that some doubtful cases were spared a laparotomy by this negative finding.

6. The patient is best examined in the position in which he arrives at the roentgen department. Thus, the patient is not disturbed, the free air is not disturbed, and therefore more accurately recorded on the roentgenogram. Very minute amounts of air are thus visualized which, in many cases, cannot be seen if the position of the patient is changed for a few brief moments preceding the roentgen examination.

7. Free air is recognized by its anatomical location, its sharp demarcation, its tendency to terminate in tapering points, and its movability.

8. The points covered in the above should apply in the diagnosis of ruptured intestines from any cause as well as from perforation of the peritoneum from the outside.

I wish to express my thanks to Dr. S. Ditkowsky, formerly of the 97th Evacuation Hospital, S.M. for his valuable assistance and suggestions in the compilation of the above material.

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Vol. 59, No. 2

THE SIGNIFICANCE OF THE WIDENED SEPTUM PELLUCIDUM

By ROBERT M. LOWMAN, M.D.,* ROBERT SHAPIRO, M.D.,† *and* LOIS COWAN COLLINS, M.D.‡

A RECENT problem in differential diagnosis presented by a widened septum pellucidum prompted a study of the significance of this finding. The purpose of this paper is (1) to discuss the importance of widening of the septum pellucidum, and (2) to consider the lesions which are said to offer difficulties in differential diagnosis.

A brief anatomic consideration of the septum pellucidum is included for the sake of clarity (Fig. 1). The septum pellucidum (lucidum) is a thin, more or less triangular membrane consisting of two glial layers covered externally with ependyma. The septum which separates the bodies of the two lateral ventricles rostrally has the following boundaries: superiorly, the ventral surface of the body of the corpus callosum; inferiorly, the rostrum of the corpus callosum and the anterior commissure; laterally, the lateral ventricles and the lateral layers of the septum pellucidum; anteriorly, the genu of the corpus callosum; posteriorly, the anterior limb and pillars of the fornix.

Normally, the two layers of the septum pellucidum are separated by a thin cavity of varying width, the cavum septi pellucidi or so-called fifth ventricle. The caudal portion of this cavity is termed the cavum vergae or sixth ventricle. However, these

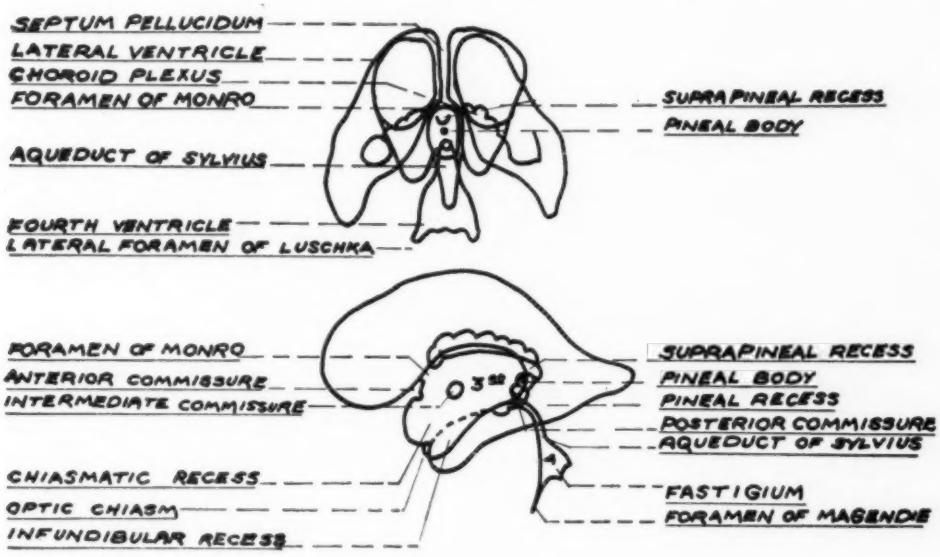

FIG. 1

structures have a different embryologic origin and are not part of the true ventricular system. They are not lined with ependyma, and may have no communication with the ventricular system.

There are two theories for the origin of the cavum septi pellucidi and the cavum vergae.[34] One theory contends that the cavities are produced by rapid widening of the lamina terminalis with resultant in-

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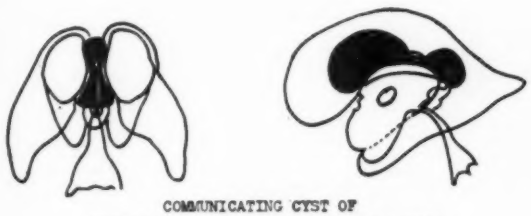
ternal tension and cavity formation during the third fetal month. The other considers the cavum to be a portion of the interhemispheric fissure. The lateral boundaries of this fissure are the medial aspects of the cerebral vesicles ventral to the caudally extending corpus callosum. The anatomic findings favor the second theory.

The major portion of the walls of these cavities is made up of glial tissue containing a moderate number of sclerotic fibrillary astrocytes with scant cytoplasm.[39] The cells lining the cavum septi pellucidi and the cavum vergae vary from low to high cuboidal in type with oval or spherical, centrally placed nuclei. Frequently, glial fibers run from the base of these cells into the surrounding glial tissue. The origin of the lining cells is in doubt. Some investigators consider them to be pia-arachnoidal inclusions but the histologic evidence is at variance with this opinion. Others suggest the possibility that they are true ependymal cells, but this also appears unlikely because the cavities are not a part of the true ventricular system, do not form a complete membrane and show no evidence of the presence of blepharoplasten when stained. Wolf and Bamford theorize that the spongioblasts lining the cavities become modified during their embryological growth to resemble ependymal cells.[39] The objection to this explanation is the fact that the major portion of the wall consists of a simple heavy glial mat of astrocyte fibers and occasional marginal astrocytes.

Young has comprehensively studied the comparative anatomy of the septum pellucidum in the lower forms as well as in mammals.[41] In the light of his investigations, the anomalies of the septum and corpus callosum can be better understood in terms of ontogenetic and phylogenetic variations. The septum serves as an intermediate station between the olfactory bulb and hippocampus, on the one hand, and between the olfactory bulb, hippocampus and the hypothalamus, on the other. In cyclostomes, the septum is entirely absent. In selechians, a basomedial cell group of the hemispheres directs itself toward the hippocampus as a result of neurobiotaxis. In the teleosts and ganoids, Young sees the homologue of the septum in the median nucleus, the pars commissuralis, the pars supra commissuralis and the pars intermedia. In amphibians (*Axolotl*) the septum shows a considerable increase in size, approaching the thickness of the ventricular walls. In reptiles, the septum is also well developed. In addition to the septal nuclei found in the amphibians, a nucleus accumbeus septi is also present, which grows from the neostriatum into the septal region. On the other hand, the septum in birds is very thin, consisting only of frontal and fimbriated divisions. Marked development of the septum is found in the lower mammals. In the marsupials, it consists of the medial and lateral nuclei, the nucleus accumbeus, the medial caudal septal nucleus, the fibers of the fornix, psalterium and secondary olfactory bundles. It lies for the most part dorsal to the corpus callosum. In higher mammals, the corpus callosum and the anterior commissure are separated and the septum principally lies ventral to the corpus callosum. In primates, the septum is elongated between the anterior commissure, fornix and corpus callosum as a result of marked growth of the latter structure anteriorly, posteriorly and dorsally. Thus are the anomalies of the septum in man reflected as normal developments in the phylogenetic scale.

Variations in the structure of the septum may be found. Infrequently, the septum pellucidum may be entirely absent.[16] When present, it is usually intact although occasionally single or multiple fenestrations occur which permit direct communication between the two lateral ventricles. On the anteroposterior encephalogram, the septum pellucidum is represented by a slit-like uniform zone of increased density outlined on either side by the air-filled lateral ventricles. The normal measurements of the septum vary from 0.9 cm. to 1.5 cm. in height and from 0.2 cm. to 0.3 cm. in width.[15]

It is to be emphasized that the slightest degree of widening of the septum pellucidum is a significant, abnormal finding which demands further investigation. Although Pendergrass and Hodes[27] state that such widening should suggest the presence of a cyst, it must be stressed that this finding is associated with a variety of lesions.

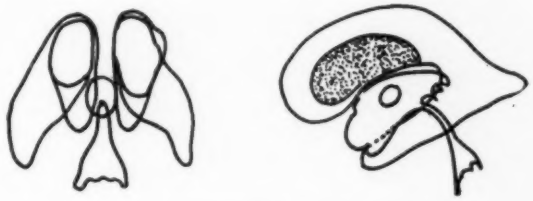


COMMUNICATING CYST OF CAVUM SEPTI PELLUCIDI AND CAVUM VERGAE

COMMUNICATING CYST OF SEPTUM PELLUCIDUM

COMMUNICATING CYST OF CAVUM VERGAE

FIG. 2



NON-COMMUNICATING CYST OF SEPTUM

SOLID TUMOR OF SEPTUM PELLUCIDUM

TUMOR OF CORPUS CALLOSUM

FIG. 3

Thus, significant widening of the septum pellucidum may be produced by the following (Fig. 2 and 3): (1) cysts of the cavum septi pellucidi; (2) tumors of the septum pellucidum; (3) agenesis of the corpus callosum; (4) tumors of the corpus callosum.

In addition, other lesions (Fig. 4 and 5) have been enumerated in the literature by various authors as offering problems in differential diagnosis:[16,25] (5) tumors of the third ventricle; (6) pinealomas; (7) tumors of the lateral ventricle; (8) midline frontal lobe tumors; (9) olfactory groove meningiomas; (10) parasagittal tumors; (11) thalamic tumors.

It is our opinion, however, that this latter group of lesions is individually distinguishable and can readily be differentiated from the lesions in the first group.

The following group comprises the lesions which produce actual significant widening of the septum pellucidum and require differentiation from one another.

CYSTS OF THE CAVUM SEPTI PELLUCIDI AND CAVUM VERGAE

Two principal types of dilatation of the cavum septi pellucidi and the cavum vergae have been described by Dandy,[9] Van Wagenen and Aird:[38] (a) communicating; (b) non-communicating.

The communicating cysts have been further subdivided into: (1) the primary

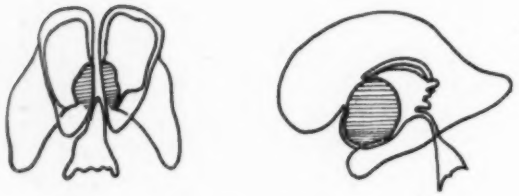
type in which there is an opening into the third or lateral ventricles presumably due to rupture of the wall because of increased intracystic pressure, and (2) the secondary or acquired type, which is associated with internal hydrocephalus.

Communicating cysts have been demonstrated frequently following encephalography or ventriculography. Although cysts of the cavum septi pellucidi and the cavum vergae usually occur together, a rare instance of a solitary cavum vergae cyst has been recorded by Leslie.[21] The cysts may vary considerably in size. In the posteroanterior view (Fig. 6*B*), the communicating cavum septi pellucidi cyst is visualized as an air containing space separating the air-filled anterior horns of the lateral ventricles. The roof of the cyst is at the same level as the roof of the lateral ventricles. The leaves of the septum pellucidum are demonstrated as linear densities between the air in the cavum septi pellucidi and the air-filled lateral ventricles. In the lateral view, the superimposed air contained in the anterior horns and bodies of the lateral ventricles makes recognition of the cyst difficult (Fig. 6*A*). However, it may be seen as a comma-shaped structure with its large diameter directed anteriorly. The anterior margin of the cyst does not extend as far forward as the anterior horns of the lateral ventricles. The tapering posterior extremity of the cyst ends in a blunt point above the junction of the aqueduct with the third ventricle.

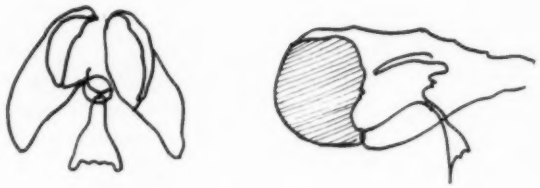
The cavum vergae cyst can be recognized on the posteroanterior encephalogram as a triangular or oblong-shaped radiolucent structure with the base directed inferiorly. The superior margin of the cyst is at a lower level than the roof of the lateral

AGENESIS OF CORPUS CALLOSUM

PINEALOMA



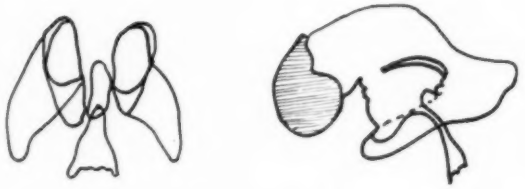
COLLOID CYST - THIRD VENTRICLE



OLFACTORY GROOVE MENINGIOMA

INTRAVENTRICULAR TUMOR
EPENDYMOMA-OF LATERAL VENTRICLE ARISING
FROM MEDIAL WALL

FIG. 4



MID-LINE FRONTAL LOBE TUMOR

FIG. 5

ventricles and the floor is also correspondingly lower than the lower border of the lateral ventricles. In the lateral view, the cavum vergae cyst is seen as an oval radiolucent structure behind the posterior limit of the cavum septi pellucidi. Because both cysts commonly occur together, they assume an hour-glass configuration in the lateral view, the area of constriction indicating the point of union.

A *B*

Fig. 6. Communicating cyst of the cavum septi pellucidi and cavum vergae. The slit-like cavum septi pellucidi and the triangular cavum vergae are outlined by air in the sagittal projection. The air delineates the comma-shaped area corresponding to the position of the septum pellucidum in the lateral view. Comparison of these studies with the line drawings in Figure 2 should be made.

Non-communicating cysts of the cavum septi pellucidi are rare. Pendergrass, Pancoast and Schaeffer[26] note that they have had no personal experience with this type of lesion, and Dyke and Davidoff[17] report only one non-communicating cyst in a series of 5,000 encephalograms. Echternacht and Campbell,[18] on the other hand, report three such cysts in their paper on midline anomalies of the brain. While communicating cysts may or may not produce clinical symptoms, the non-communicating variety is frequently associated with convulsions because of obstruction of the foramina of Monro and the resultant increased intracranial pressure.

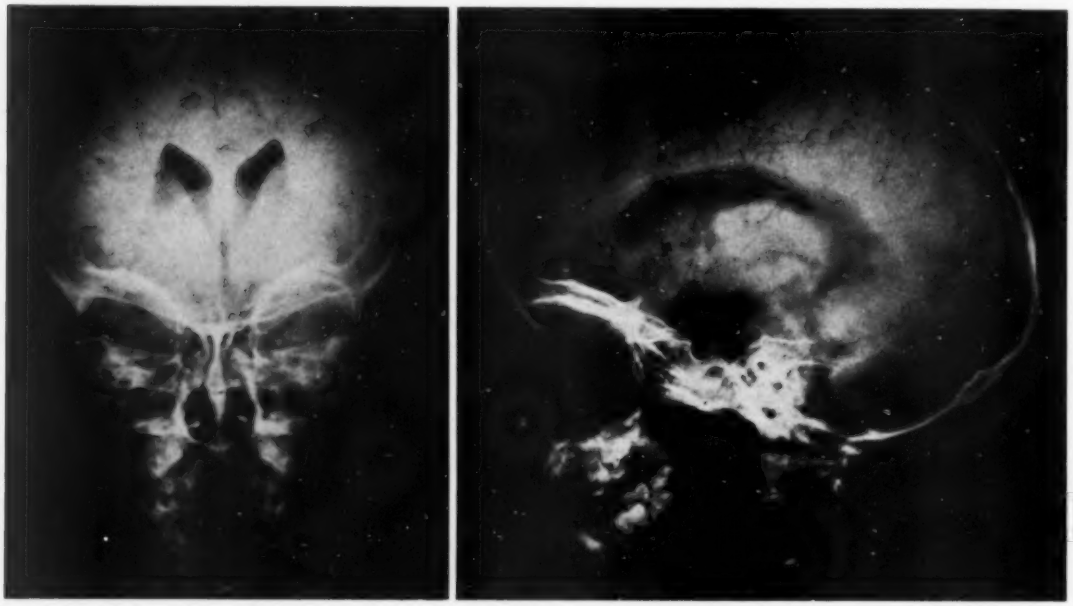
In the encephalogram, the lateral ventricles may show dilatation because of the obstruction of the foramina of Monro or the aqueduct. The radiopaque cystic mass usually encroaches upon the medial walls of the lateral ventricles in a uniform manner, and thereby produces separation of the lateral ventricles (Fig. 7). However, rarely, the encroachment of the cyst may be more marked on one side. Frequently, there is downward displacement of the pineal body and the roof of the third ventricle. In the lateral view, the appearance of the non-communicating cyst is similar to that described for the air-filled communicating cysts except that the former is radiopaque. For this reason, their demonstration in the lateral view is variable depending upon the size of the filling defects produced by the cysts in the lateral ventricles. While even small defects can be readily recognized in the posteroanterior projections, only sizable defects will be recognized in the lateral views.

Tumors of the Septum Pellucidum

The tumors of the septum pellucidum are rare. A thorough search of the Ameri-

can literature has revealed a case of a midline ependymoma arising from the septum reported by Bailey and Cushing.[2] Similarly, relatively few cases are reported in the English literature. Thus, a case of a midline astrocytoma described as a tumor originating in the corpus callosum and invading the septum is described by Purves-Stewart.[28] None of the above reports is accompanied by pneumographic studies. The photographs of the brain sections if translated into air studies would simulate a septum pellucidum cyst or tumor. Busch[5] in 1944, reviewing the technique of intracranial surgical approaches, also described a tumor of the septum but the histopathology of this tumor is not recorded. Excluding the cases described above, only 8 lesions of this type could be found in a survey of the world literature.[6,7,25,29,33,37,40] Five of these were reported as gliomas (one of these was classified as a fibrillary glioma), one was reported as glioblastoma, and the remaining two as fibrillary astrocytomas. Only primary tumors originating in the septum are included in this grouping. Therefore, the case described by Purves-Stewart is not listed as a septal tumor.

A study of these cases failed to demonstrate any clinical or neurological findings which could be of aid in localization. Pendergrass, Pancoast and Schaeffer[26] state that tumors of the septum produce irregular distortion of the contours of this midline structure. Thus, they believe it possible to differentiate between tumors and cysts, since the latter produce a uniform smooth expansion of the septum. When irregularity of the widened septum is found, tumor is more likely to be present. That tumors of the septum do not necessarily produce irregularity is well demonstrated by the first case (Case 1). Because of the rarity of these tumors and the unique roentgen findings demonstrated following pneumographic studies, the first case is reported in detail.



A *B*

FIG. 7. Non-communicating cyst. The widened septum pellucidum (6 mm.) is shown in the sagittal views. In the lateral view, the arrows outline the density formed by the cyst which is superimposed upon the anterior horns and the anterior portions of the lateral ventricles. (This case is not confirmed.) (The illustration is reproduced with the kind permission of A. P. Echternacht and J. A. Campbell, and *Radiology*, 1946, *46*, 119–131.)

CASE 1. C. G., a male, aged thirty-four,

chemist, was admitted to the Grace Hospital on December 14, 1942, because of headaches of three months duration. The headaches, insidious in onset, were most frequently frontal, but were occasionally noted in the occipital and biparietal areas as well. Ten days prior to admission, persistent projectile vomiting appeared. Two days later, during a conversation, he suddenly lost consciousness for an hour. Upon responding, he was dazed and could not remember the period of unconsciousness. For the past three months also, there had been impairment of memory for recent events and some personality changes characterized chiefly by irritability.

Seven months ago, the patient was placed on an ulcer regimen by his physician because of nausea, anorexia and a weight loss of 22 pounds. No vomiting was present at that time and he soon regained the lost weight.

The past medical history included measles, pneumonia, bronchitis and pertussis in childhood, a sacroiliac strain in 1939 and removal of a lipoma of the right shoulder in 1938. A grim coincidence was the patient's statement that his father had a "tumor at the base of the brain" removed. The details of the operative procedure could not be obtained.

Physical examination was essentially negative except for hyperactive but symmetrical deep reflexes and a positive bilateral Hoffman sign. No Babinski was present and the eye grounds were normal. The significant laboratory findings were as follows: the Wassermann reaction was negative; the red blood cell count was 4.54 million per cu. mm. with 80 per cent hemoglobin; the white blood cell count was 12,000 per cu. mm. with 70 per cent segmented polymorphonuclear leukocytes, 7 per cent nonsegmented polymorphonuclear leukocytes, 17 per cent lymphocytes and 6 per cent monocytes. The blood sugar was 92 mg. per 100 cc. The non-protein nitrogen was 35 mg. per 100 cc.

The lumbar puncture on December 15, 1942, showed an initial cerebrospinal fluid pressure of

Fig. 8. Case 1. Tumor of the septum pellucidum. The posteroanterior (*A*) and anteroposterior (*B*) projections are shown. The symmetrically widened septum pellucidum measured 6 mm. in the posteroanterior view. Note the marked similarity in the posteroanterior view of the non-communicating cyst in Figure 7. Pathologic examination demonstrated a diffuse fibrillary astrocytoma of the septum in this case.

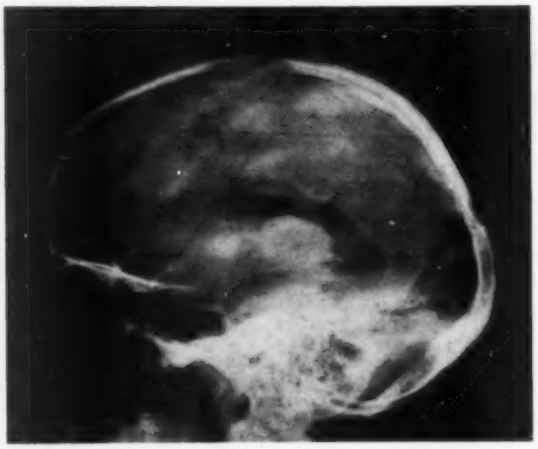


FIG. 9. Case 1. The lateral view demonstrates the irregular scalloped defects in the roof and the anterior horns of the lateral ventricles.

525 mm. H_2O with no block. The fluid was translucent, colorless, contained 1 monocyte per high power field and a total protein of 14 mg. per 100 cc. The colloidal gold test was negative.

Roentgen examination of the skull at this time showed some decalcification of the posterior clinoid tips, increased digital markings and slight posterior and downward displacement of the pineal body.

Re-examination of the ocular fundi on December 20 showed definite blurring and congestion of the superior nasal margin of the right fundus. On December 30, the patient complained of severe headache. Fundoscopic examination at this time showed early choking of both discs and visual field studies revealed full peripheral range with small "blind spots" bilaterally. Ventriculography was attempted on January 7, 1943, but was not entirely satisfactory because of the introduction of an insufficient quantity of air. This study was repeated on January 17 and definite widening of the septum pellucidum was noted, suggesting the diagnosis of an infiltrating tumor in this area (Fig. 8 and 9). Another lumbar puncture on January 19 revealed an initial pressure of 280 mm. H_2O with a cell count of 6 lymphocytes per high power field and a total protein of 51 mg. per 100 cc.

On January 22, an electroencephalogram showed 8–9 per second and 5–6 per second wave frequencies mixed in all leads. The left occipital, and to a lesser extent, the left temporal leads showed numerous 2–3 per second waves on monopolar recording. On bipolar recording, there was out-of-phase activity pointing to a left occipital focus. Lumbar puncture was repeated on February 3 because of the unusual severity of the patient's headaches. The initial cerebrospinal fluid pressure was 220 mm. H_2O and the total protein was 30 mg. per 100 cc. On February 9, ventriculography was repeated but showed no significant change since the previous study. A left frontal flap was then made, the dura opened and the brain explored. No abnormalities could be found in the prefrontal area, at the base of the brain or between the hemispheres. Internal decompression was deemed advisable and the left prefrontal lobe was resected.

The patient died on February 11, 1943. At autopsy, gross examination of the brain, after fixation in formalin, showed only uniform diffuse widening of the septum pellucidum. No localized tumor masses were noted. Numerous microscopic sections, however, demonstrated the presence of extensive tumor invasion with coalescent sheets of fibrillary astrocytes. In some areas, a glial stroma between the astrocytes could be seen.

Comparative illustrations demonstrate that the appearance of the widened septum pellucidum produced by tumor and non-communicating cysts can be indistinguishable (compare Fig. 7*A* and 8*A*). It is obviously of considerable importance, therefore, to be able to differentiate these lesions because of the marked difference in prognosis. Dandy,[8,9] and Echternacht and Campbell[18] have reported cases in which non-communicating cysts have been transformed into the communicating variety as a result of accidental puncture of the cyst wall by the exploring trocar. We believe that such a procedure is of paramount diagnostic importance and should be employed in any mass lesion of the septum visualized as an area of increased density in the air studies. In this way, a non-communicating cyst may be converted into a cyst of the communicating type, thus permitting easy differentiation.

CASE II. M. S., male, aged thirty-five, was admitted to the Neurological Institute on Feb-

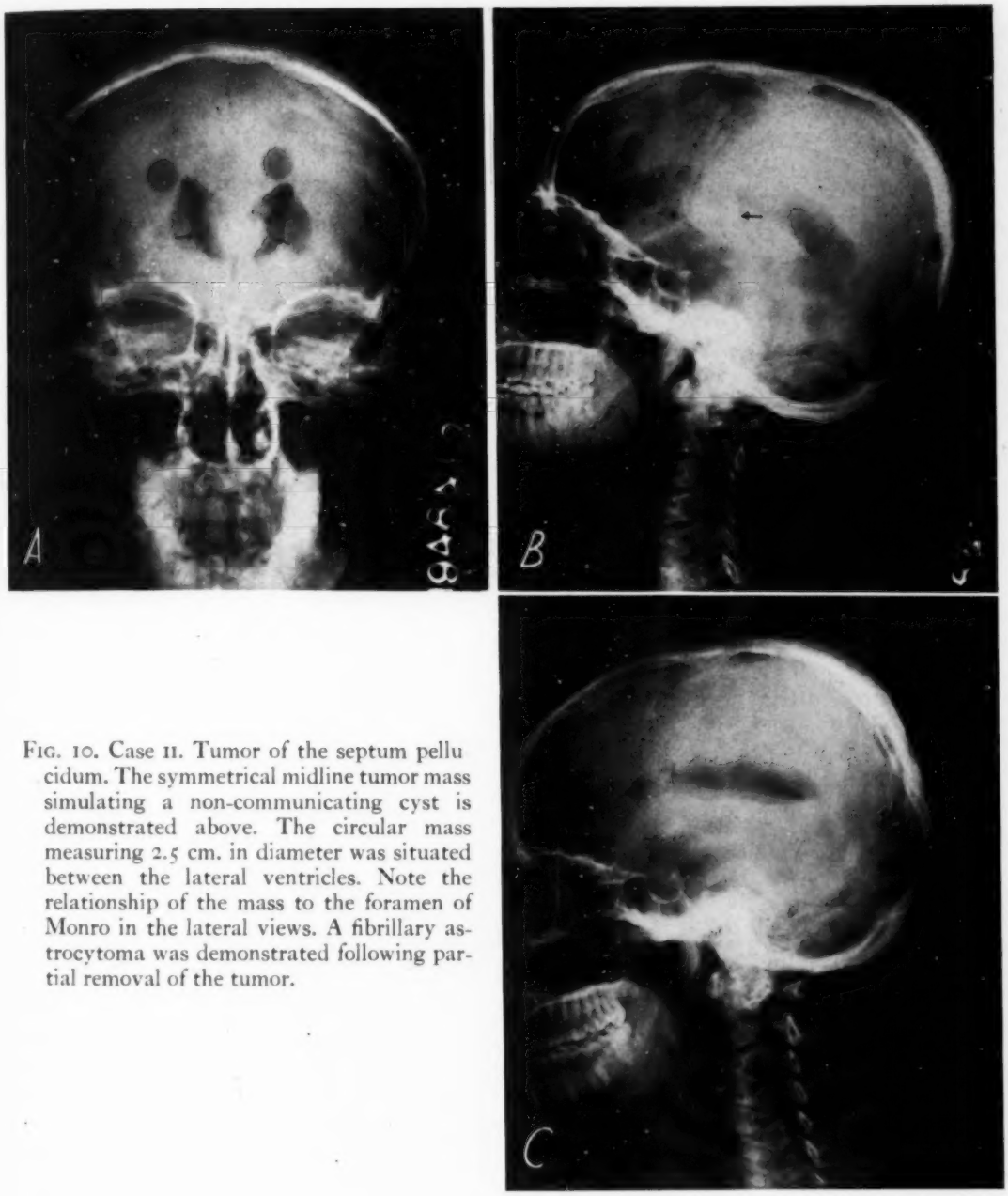


Fig. 10. Case 11. Tumor of the septum pellu cidum. The symmetrical midline tumor mass simulating a non-communicating cyst is demonstrated above. The circular mass measuring 2.5 cm. in diameter was situated between the lateral ventricles. Note the relationship of the mass to the foramen of Monro in the lateral views. A fibrillary astrocytoma was demonstrated following partial removal of the tumor.

ruary 13, 1931, complaining of intermittent headaches since 1922, which had been steadily increasing in severity, particularly for the five weeks prior to admission. He had had one generalized epileptic seizure in 1922. Five weeks prior to admission, he first noticed dizziness followed by impaired hearing in the right ear. Three weeks later, before admission, he began to have blurred vision accompanied by vomiting five days before entering the hospital. There was a weight loss of 10 pounds in the two weeks prior to admission.

The physical examination showed uncertainty of gait, no ataxia, fine tremors of fingers of the right hand, exaggerated reflexes, bilateral papilledema with hemorrhages and impaired hearing.

The spinal fluid globulin and Wassermann reaction were negative. The protein was 24 mg. per 100 cc.

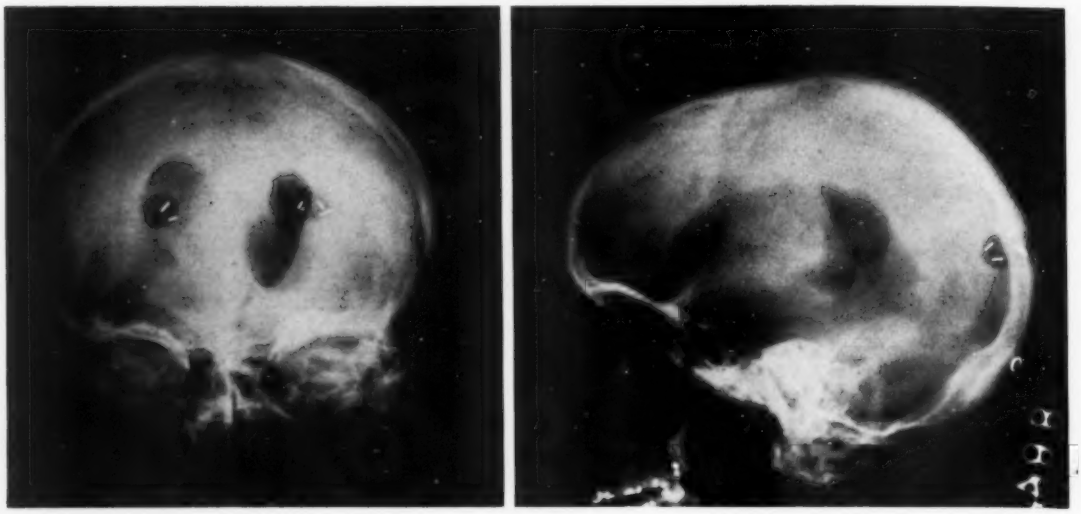


FIG. 11. Case III. Tumor of the septum pellucidum. The tumor produced a concave impression in the medial margins of the ventricles. Both lateral ventricles were dilated because of the obstruction at the foramen of Monro. This was interpreted as a non-communicating cyst of the cavum septi pellucidi and an unspecified glioma was found at operation.

Ventriculographic studies demonstrated a sharply defined circular mass 2.5 cm. in diameter lying between the lateral ventricles at the foramen of Monro (Fig. 10).

At operation, on March 9, 1931, four small nodules varying from 5 to 10 mm. in size were noted in the leptomeninges, each lying adjacent to a large vein. At the time of operation, these were reported as lymphosarcoma, and therefore the flap was closed without making any attempt to explore the mass in the lateral ventricles. Subsequent histopathologic study did not confirm the diagnosis of lymphosarcoma.

More recent review of the slides of the specimens taken at this operation reveals that these nodules were probably arachnoid cell clusters and not lymphosarcoma.

The patient was given roentgen treatment directed to the interventricular mass, as follows:

Between March, 1931, and June, 1934, the patient received a total of 9,300 r to the right frontoparietal area (centered for foramen of Monro); 8,250 r was delivered to the left frontoparietal area and 4,500 r to the midline forehead. Treatments were given in doses varying from 300 to 600 r (measured in air) per field per day, in series varying from 750 to 2,400 r total per field. The usual interval between series was two to three months.

Following this, he did well until 1933, at which time he was readmitted because he had had a convulsion, during which his eyes had turned to the left. This had occurred following a roentgen treatment. During this admission, several nodules over the anterior aspects of the thighs were biopsied, on the possibility that neurofibromata might be present, but these nodules proved to be lipomata. He had no further convulsions and was discharged in two weeks.

In June, 1934, he was readmitted because of frequent convulsions, impaired memory, and emotional instability.

A ventriculogram showed little change since the original study in 1931. The interventricular mass was present as before and essentially the same size. It was interpreted as a non-communicating cyst of the septum pellucidum.

Operation on April 15, 1935, revealed a reddish-brown tumor mass along the inferior margin of the septum pellucidum. It was partially removed, its position making complete removal impossible.

The histopathological examination revealed fibrillary astrocytoma.

The patient did well postoperatively, but the mental condition did not improve. He died in another hospital the following year. Autopsy was not performed.

It seems fair to assume, in this case, that the failure of the tumor to increase in size in four years (as judged by air studies) was due to the roentgen treatment.

Case III. M. L., female, aged twenty-eight, was admitted to the Neurological Institute on May 31, 1932, because of frontal headaches. These had started gradually about six months prior to admission, and had been associated with a painful sensation over the eyes. Two months prior to admission, she had become generally weak, experienced some difficulty in walking, and complained of ringing in the ears. One month prior to admission, she had to give up her work because of weakness and drowsiness.

Physical examination revealed a slight over-adduction of the right leg in walking, slight awkwardness of the left hand, but no abnormal reflexes. The fundi showed blurring of the discs with distended veins and rather small arteries; one diopter of papilledema was noted. The visual fields showed enlargement of the blind spots. There was a slight right lower facial weakness.

The ventricular spinal fluid showed a protein of 76 mg. per 100 cc., and 2 plus globulin. The serology was negative.

Roentgenograms of the skull showed a slightly enlarged sella with atrophic dorsum indicating increased intracranial pressure.

Ventriculographic studies showed that both lateral ventricles were separated, apparently by a mass approximately 4.5 cm. in diameter, which caused a concave impression in the medial margins of the ventricles. The mass lay in the position of the septum pellucidum and was interpreted as a non-communicating cyst of the cavum septi pellucidi. Both lateral ventricles were dilated, apparently due to the obstruction at the foramen of Monro (Fig. 12).

On June 14, 1932, a right osteoplastic flap was turned, and exploration of the septum pellucidum was completed. Deep in the midline, a tumor mass was encountered.

On puncture of the mass, there was so much venous bleeding encountered that it was considered unwise to proceed. When bleeding was controlled, the flap was closed.

The biopsy specimen was unsatisfactory for specific diagnosis, but there was no doubt that it was neoplastic tissue. The pathologist con-

Fig. 12. Complete agenesis of the corpus callosum. The sagittal projection demonstrates the separation of the lateral views, the concavity of the medial borders and pointing of the dorsal margins of the lateral ventricles and the dilatation and elevation of the third ventricle. Interhemispheric and subdural air obscures the lateral view so that the radial arrangement of the sulci cannot be seen satisfactorily.

sidered oligodendroglioma as the most likely diagnosis but the specimen was inadequate for definite classification.

The summary of the roentgen therapy follows: From June, 1932, to October, 1932, she had a total of 2,000 r to the right frontal area; 2,000 r to the left frontal area, and 1,600 r to the mid forehead. This was given in two series, one in June and one in October. Treatments were given at the rate of 200 r (measured in air) per day.

After operation and roentgen treatment, the patient was remarkably improved, and remained free of complaints during the next six years. The patient ceased to return for follow-up visits in 1938.

Although the histopathology of this tumor is not clear, it seems probable that it was a slow-growing glioma, that is, either oligodendroglioma or astrocytoma.

It is important to note that although Cases II and III were both confirmed tumors, the preoperative roentgen diagnosis in each case was that of cyst of the septum pellucidum. It is our impression that the astrocytoma or oligodendroglioma whether originating in the lower part of the corpus callosum or in the septum proper is more likely to produce a symmetrical midline tumor mass resembling a non-communicating cyst than an ependymoma. This is borne out by the astrocytomas presented by Purves-Stewart and in this report. These masses were midline and symmetrical. On the other hand, 2 cases of midline ependymoma which have been operated upon at the Neurological Institute (Dr. Benno Schlesinger) and observed by one of us (L.C.C.) have been asymmetrical. This asymmetry is best explained by the fact that ependymomas must arise from one side or the other of the septum. The tumor probably grows freely filling the ventricle on the side of origin. When the tumor is impeded by the relative resistance of the lateral wall of the ventricle, the mass then bulges into the opposite ventricle. As the ependymomas reach sufficient size, however, they may fill both ventricles but are somewhat larger on the side on which they first arose and grew.

AGENESIS OF THE CORPUS CALLOSUM

The corpus callosum develops as an outgrowth of the lamina terminalis between the third and fifth fetal months. During the first three weeks of fetal development, the cerebral hemispheres and the ventricular system form a single structure. From the fourth to the twelfth week, the longitudinal fissure appears, dividing the cerebral hemispheres in two. During the fourth month, the anterior commissure and genu of the corpus callosum are differentiated. Various degrees of maldevelopment of the corpus callosum may occur, depending upon the stage of arrest in embryonic growth. These abnormalities are frequently associated with defects in the neighboring structures. Thus, the anomaly may range from a minor defect in one portion of the corpus callosum to absence of the entire corpus. Absence of the anterior commissure, portions of the fornix and the septum pellucidum have also been reported in these cases.

The characteristic pneumographic changes indicative of agenesis of the corpus callosum have been described by Davidoff and Dyke[13] as follows: (1) marked separation of the lateral ventricles; (2) angular dorsal margins of the lateral ventricles; (3) concave mesial borders of the lateral ventricles; (4) dilatation of the caudal portions of the lateral ventricles; (5) elongation of the interventricular foramina; (6) dorsal extension and dilatation of the third ventricle; (7) radial arrangement of the mesial cerebral sulci around the roof of the third ventricle and extension of these sulci through the zone usually occupied by the corpus callosum.

The radially arranged convolutions and sulci found on the medial aspect of the brain associated with agenesis are thought to represent the anomalous preservation of these intracranial structures existing prior to the formation of the corpus callosum in the third month of fetal life

Bunts and Chaffee[4] state that agenesis of the corpus callosum may be confused with a cavum septi pellucidi communicating

Fig. 13. Tumor of the corpus callosum. The anteroposterior projection following ventriculography shows marked separation of the lateral ventricles. In the lateral projection, deformity and obliteration of the anterior portions of the lateral ventricles is shown. Pathologic classification of an astrocytoma following transfrontal craniotomy confirmed the preoperative diagnosis.

cyst. Davidoff and Dyke,[13] and Hyndman and Penfield[20] have reported cases of agenesis of the corpus callosum which were misinterpreted as cysts of the cavum septi pellucidi. However, the angular dorsal margins of the lateral ventricles, the dilatation of the caudal portions of the lateral ventricles and radial arrangement of the mesial cerebral sulci should serve to differentiate agenesis of the corpus callosum from communicating cysts of the cavum septi pellucidi.

Sosman[32] has made the interesting observation that agenesis of the corpus callosum may be associated with a midline intracranial lipoma.

TUMORS INVOLVING THE CORPUS CALLOSUM

While congenital anomalies arising from the midline structures are rare, it is well to recognize that tumors originating in the corpus callosum are likewise uncommon. Thus, Dyke and Davidoff[17] have made the diagnosis of a corpus callosal tumor 8 times in a series of 3,000 air studies. Pathologic verification of the tumor growth in 5 cases of this series is reported. Dyke and Davidoff enumerate the characteristic pneumoencephalographic findings diagnostic of tumors of the corpus callosum as follows: (1) separation and asymmetrical distortion of the lateral ventricles without displacement of the ventricular system as a whole to either side; (2) a sharply circumscribed defect in the dorsal margin of one or both lateral ventricles; (3) occasional failure of one lateral ventricle to fill with gas; (4) distortion of the sulci and convolutions on the medial aspect of the brain; (5) deformity or obliteration of the dorsal and rostral portions of the third ventricle.

Since this tumor arises above, and infiltrates between, both lateral ventricles, separation of the lateral ventricles without lateral displacement of the ventricular sys-

tem is found (Fig. 13). If the growth of the tumor is equal in all directions, the maximum separation of the lateral ventricles is noted in their dorsal portions. However, if the principal expansion of the tumor is directed ventrally, then the lateral ventricles are equally separated for the entire ventrodorsal distance. Since the neoplastic growth does not follow an orderly pattern, one side is usually involved more extensively than the other, thus accounting for the asymmetrical separation of the lateral ventricles in the anteroposterior view. The occasional failure of one lateral ventricle to fill with gas following unilateral ventriculography or pneumoencephalography is the result of obstruction to one or both foramina of Monro when the tumor is localized to the rostral portion of the corpus callosum. If the air enters the third ventricle, a deformity in the dorsal and rostral portion of this structure may be seen. The distortion and dorsal displacement of the angulate and callosal sulci add further evidence to the presence and size of these tumors.

DIFFERENTIAL DIAGNOSIS

These lesions are not associated with any characteristic neurologic syndromes. Therefore, it is of paramount importance to recognize the pneumoencephalographic changes which permit differentiation, since this is the only means by which the proper diagnosis can be established.

Tumors of the corpus callosum can be distinguished from communicating cysts of the cavum septi pellucidi with comparative ease because of the presence of air in the midline cystic cavity. In addition, the following characteristics, which are pathognomonic of corpus callosal tumors, serve to differentiate these lesions from non-communicating as well as communicating septal cysts:

(1) Callosal tumors produce asymmetrical, irregular separation of the lateral ventricles in the anteroposterior view. This is in contradistinction to the smooth, symmetrical, concave mesial borders of these ventricles found in septal cysts.

(2) The deformity of the dorsal aspect of the lateral ventricles and the changes in the callosal and cingulate sulci seen with callosal tumors in the lateral view are not found in cases of septal cysts.

In discussing tumors of the septum pellucidum and the corpus callosum, it is important to emphasize that it is difficult to classify these tumors accurately. This presentation is based strictly on a classification by localization. Thus, a tumor from the adjacent lobes invading the corpus callosum, or even a septal tumor invading the corpus callosum could all be classed as a corpus callosal tumor. Similarly, this is true of the septum pellucidum. Unless a tumor is localized strictly to one structure i.e. the corpus callosum or the septum, it may be impossible to determine its site of origin by any method of examination including autopsy. The histopathological types of tumor in these regions are the same as in other parts of the brain.

Primary tumors of the septum and noncommunicating cysts may produce a similar roentgen appearance. Therefore, the diagnostic criteria enumerated under noncommunicating septal cysts also serve to differentiate these lesions from tumors of the corpus callosum. It is important, here, to re-emphasize the importance of puncture of a mass lesion of the septum pellucidum by means of a trocar in order to permit entrance of air into a non-communicating cyst, thereby differentiating it from a tumor of the septum pellucidum.

Differentiation of agenesis of the corpus callosum from callosal tumors may be established by the following characteristics:

(1) In agenesis, the separation of the lateral ventricles is symmetrical whereas corpus callosal tumors produce asymmetrical separation of the lateral ventricles.

(2) The dorsal margins of the lateral ventricles are characteristically pointed and the caudal portions of the lateral ventricles are dilated in the anteroposterior view in agenesis, whereas these findings are not present in callosal tumors.

(3) The sulci in the medial aspect of the

brain course ventrodorsally through the zone normally occupied by the corpus callosum.

(4) The defect on the dorsal aspect of the lateral ventricles seen in the lateral view in callosal tumors is absent in agenesis.

(5) In the plain roentgenograms of the skull, evidence of increased intracranial pressure may be noted in tumors of the

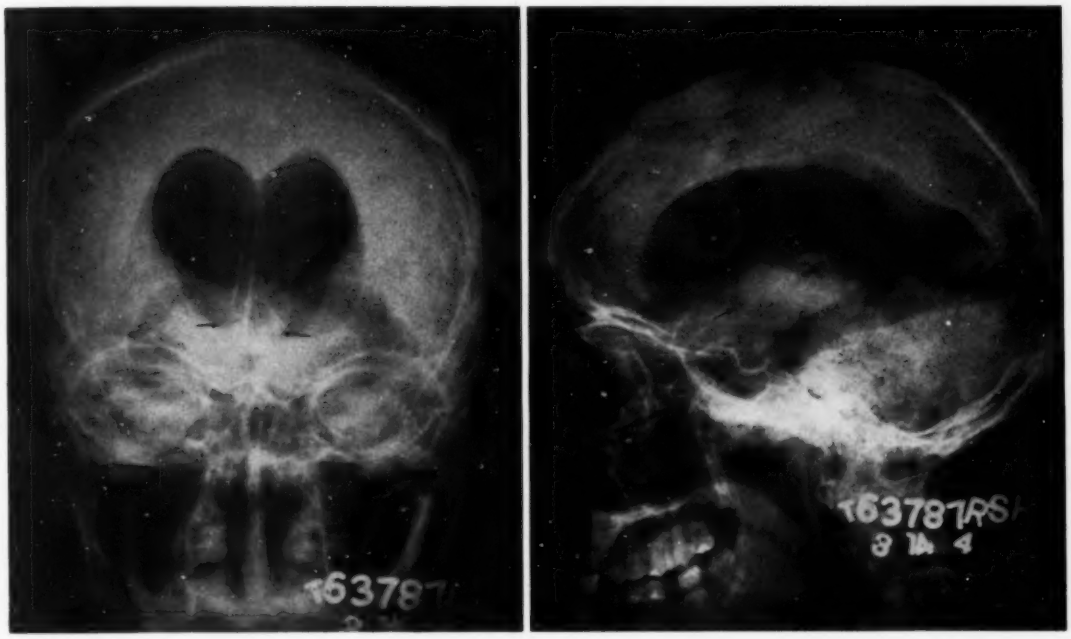


Fig. 14. Colloid cyst of the rostral portion of the third ventricle. The midline mass lying in the rostral portion of the anterior portion of the third ventricle is shown in the posteroanterior and lateral views. Obstruction in the foramina of Monro has produced the dilatation of the lateral ventricles.

corpus callosum while such changes are absent in agenesis.

(6) The third ventricle is elongated and high.

Although various investigators have included the second group of tumors among the lesions which offer differential diagnostic problems, they can be distinguished from the midline lesions described in the first group. In addition to the conventional pneumographic roentgen studies, the diagnosis of these lesions is facilitated by laminagraphy[19,23,35] and the various positional techniques recommended by Twining[36] for visualizing the third ventricle and aqueduct.

TUMORS OF THE THIRD VENTRICLE

A number of cases of tumors of the third ventricle has been reported by Dandy,[8,11] Zimmerman and German[42] and Davidoff and Dyke.[14]

The benign tumors of the third ventricle are usually of three varieties: (1) so-called colloid cysts in which the cyst wall is composed of cuboidal or columnar ciliated epithelium and the stroma consists exclusively of collagenous connective tissue; (2) bucconeural pouch tumors or adamantinomas in which the histological structure demonstrates the cyst wall to be composed of a multilayered squamous epithelium arranged in papillary processes; (3) epidermoid cysts in which the cyst wall is composed of stratified squamous epithelium and masses of lipoid-containing phagocytes, cellular debris and cholesterol crystals.

Since many of these tumors are of benign character and amenable to cure following surgical intervention, the diagnosis of such lesions is of the utmost practical impor-

tance. On the anteroposterior encephalogram, the appearance produced by colloid cysts of the third ventricle may superficially resemble that found in communicating septal cysts. This is due to the fact that the tumor produces obstruction and internal hydrocephalus with resultant dilatation and upward displacement of the third ventricle. The latter structure may be mistaken for a cyst of the septum pellucidum. In these hydrocephalic lateral ventricles due to obstruction of the foramen of Monro, there may be a perforation of the septum pellucidum. Hence, free passage of air between the lateral ventricle does not exclude obstruction at the foramen.

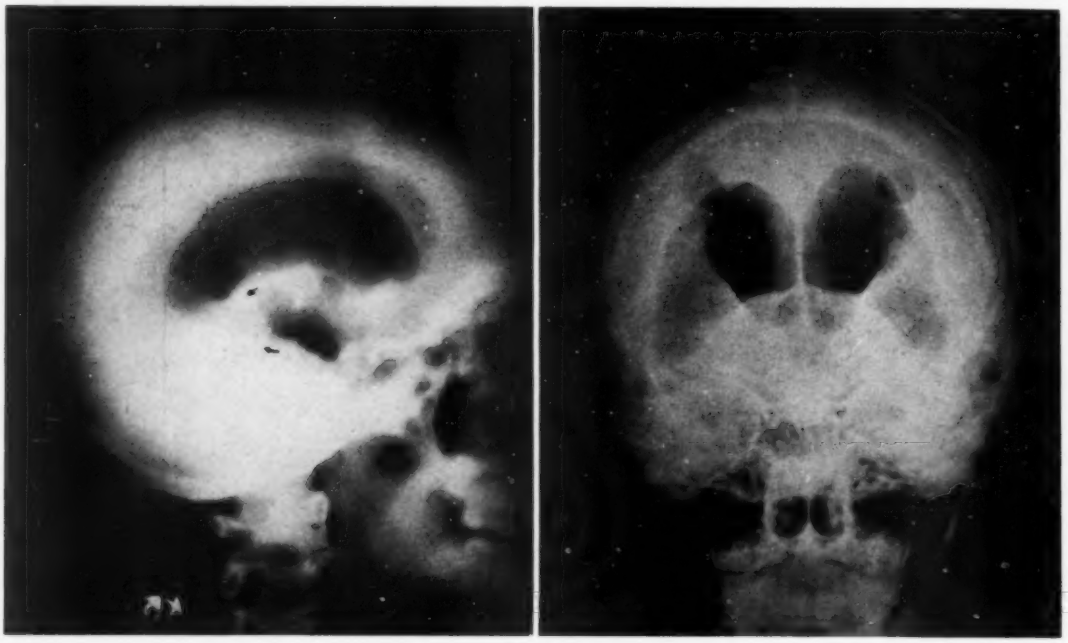


FIG. 15. Pinealomas. The midline mass situated in the posterior portion of the third ventricle is demonstrated by posteroanterior and lateral views. The crescentic bulge in the posterior portion of the third ventricle is well demonstrated in the lateral view. Note the calcification in the pineal area.

However, closer inspection of the anteroposterior films frequently demonstrates a filling defect in the third ventricle.[14] The border of the air posterior to the filling defect has a straight or concave margin. There is no problem in differential diagnosis on the lateral films. In these films, the filling defect is represented by an area of increased density in the anterior portion of the third ventricle which can readily be made out.

When ventriculography is performed and a single puncture is done, air may fail entirely to pass into the other lateral or third ventricle, or may do so with considerable difficulty. There may be deviation of the septum pellucidum to one side and again the filling defect in the anterior portion of the third ventricle can be noted. When double ventricular puncture is done, the sharp demarcation of the air shadow in the foramen of Monro as well as the filling defect can be seen.

PINEALOMAS

These tumors usually present characteristic changes. Because of their location in the midline of the posterior wall of the third ventricle just above the aqueduct, these masses encroach upon and deform the posterior junction of the ventricle obliterating the suprapineal recess. The tumors

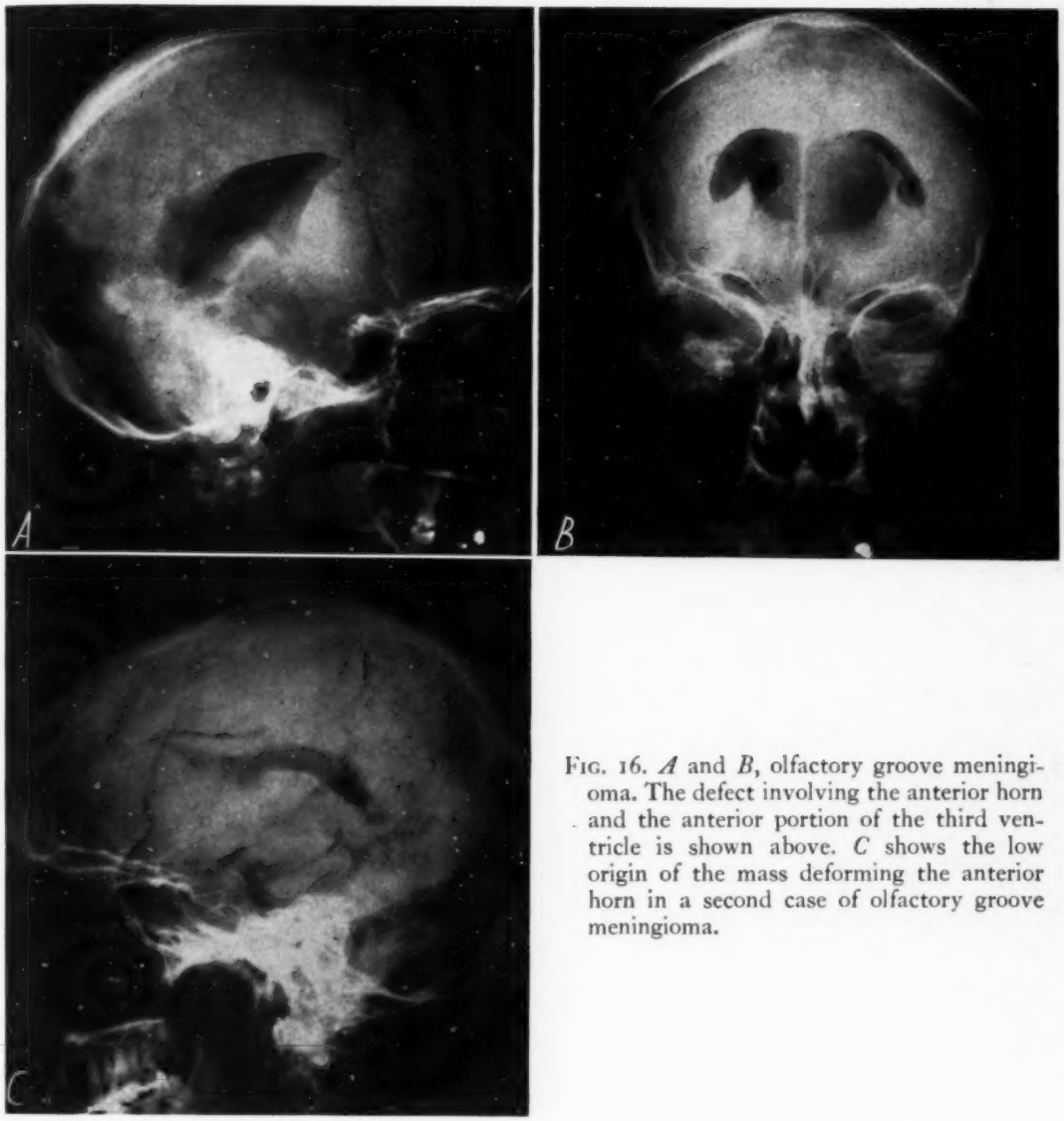


FIG. 16. *A* and *B*, olfactory groove meningioma. The defect involving the anterior horn and the anterior portion of the third ventricle is shown above. *C* shows the low origin of the mass deforming the anterior horn in a second case of olfactory groove meningioma.

form a filling defect or a cresentic bulge into the posterior portion of the third ventricle.[15] The early obstruction of the aqueduct causes the obstructive hydrocephalus. The resultant obstructive hydrocephalus produces symmetrical expansion and separation of the lateral ventricles. The recognition of the filling defects in the posterior portion of the third ventricle in the lateral view can readily be made if complete filling of this ventricle with air has been obtained. The employment of positional maneuvers recommended by Twining, the head manipulations advised by Lysholm[24] and laminagrams are important for the visualization of the lesions in this area. The presence of calcification in the pineal tumor is also of localizing value.

TUMORS OF THE LATERAL VENTRICLES

Tumors originating from the medial aspect of the lateral ventricles separate the lateral ventricles and encroach upon the third ventricle. Ependymomas arising in these areas may produce internal hydrocephalus by blocking off the foramina of

Monro. Thus, they can be confused on the posteroanterior roentgenogram with a non-communicating cyst, or tumor of the septum. Usually, however, they are asymmetrical and deform only a single ventricle. In the lateral view, an opaque filling defect in one or the other air-filled ventricles serves to differentiate this lesion from primary lesions of the septum.

MIDLINE FRONTAL LOBE TUMORS

Frontal lobe tumors extending beyond the midline and tumors arising from the falx cerebri anteriorly produce separation of the anterior horns of the lateral ventricles which may be indistinguishable on the posteroanterior encephalogram from the appearance due to septal lesions. In the lateral view, however, characteristic filling defects in the anterior horns can be seen which aid in the differentiation of these lesions.

OLFACTORY GROOVE MENINGIOMAS

These tumors, with their associated hyperostosis and other characteristic bone changes, should cause no confusion, even though they may grow to a large enough size to produce some separation of the anterior horns of the lateral ventricles.

It is important to point out that the origin of the olfactory groove meningiomas is below the level of the lateral ventricles whereas septal tumors are at the level and callosal tumors are above the level of the ventricles. The low origin of the olfactory groove meningiomas is usually demonstrable in the type of defect in the anterior horn and anterior part of the third ventricle (Fig. 16).

PARASAGITTAL TUMORS

Tumors arising dorsal to the corpus callosum produce displacement of the ventricles to the side opposite the tumor. The lateral ventricles are not separated and the homolateral ventricle is flattened and depressed.

TUMORS OF THE THALAMUS

Tumors of the thalamus which produce bilateral equal invasion obliterate the posterior portion of the third ventricle. This is well demonstrated in the lateral view. The suprapineal recess, however, is not deformed. In the sagittal view, there is separation of the lateral ventricles which superficially resembles a non-communicating septal cyst. Moreover, it should be noted that most thalamic tumors are unilateral and these, of course, present no problem.

SUMMARY

(1) The embryology, comparative anatomy, normal anatomy and measurements of the septum pellucidum are reviewed.

(2) The significance of widening of the septum pellucidum and the various lesions which may produce this finding are discussed.

(3) Two groups of lesions are presented: (a) The first group includes cysts of the cavum septi pellucidi, tumors of the septum pellucidum, agenesis of the corpus callosum and tumors of the corpus callosum. The criteria for the roentgen diagnosis of these lesions is noted and their differential diagnosis is discussed. (b) The second group is composed of a heterogeneous collection of lesions which offer few problems in differential diagnosis. The characteristic roentgen features of the latter group of lesions are also presented.

(4) Three cases of tumor of the septum pellucidum are presented with accompanying air studies. No previous report of such cases has been found in the American literature.

(5) A procedure for distinguishing solid tumors from cysts is suggested, i.e. attempted puncture of the septum pellucidum by an exploring trocar.*

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VISUALIZATION OF THE ROKITANSKY-ASCHOFF SINUSES OF THE GALLBLADDER DURING CHOLECYSTOGRAPHY

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A SEARCH of the literature revealed no record of the demonstration of Rokitansky-Aschoff sinuses during cholecystography, and since it produces a unique appearance that seems to be characteristic, a case demonstrating this phenomenon is being reported together with a discussion of the condition. Of secondary interest in this case is the occurrence of a double gallbladder shadow produced by a stricture of the gallbladder.

CASE REPORT

A white female, Mrs. J. B., aged twenty-seven, was referred for an intravenous urogram because of pain in the right side. This study revealed a marked hypogenesis of the right kidney with compensatory hypertrophy of the left kidney. It was then felt that the patient's symptoms might be biliary in origin, and a cholecystogram was made. This revealed a double gallbladder shadow of a slightly less than normal degree of density. An unusual narrow concentric shadow of dye was noted around one of the gallbladder shadows. The examination was repeated with 9 grams of priodax in an attempt to get as dense a gallbladder shadow as possible in order to try to visualize an accessory cystic duct or a communication between the two pouches, and the result is shown in Figure 1. Various projections were employed, including the erect (Fig. 2) and a very marked Trendelenburg, but no communication between the two pouches could be demonstrated. The dye in the lower pouch was somewhat more concentrated than that in the upper one. After a fat meal, both pouches contracted, the upper one more than the lower. There was no evidence of calculi. The reason for this report, however, is the peculiar rim of dye passing in a layer concentrically around the surface of the lower pouch, as seen in Figures 1, 2, 3, 4 and 5. This finding was constant and was seen in each of three cholecystographic examinations done on this patient. The concentric ring is more apparent when the gallbladder is contracted after a fat meal. Calcification in the wall of the gallbladder was not a factor here since no shadow was seen on the preliminary plain film. No adequate explanation could be given for it, and the situation was confused by the fact that we were trying to demonstrate an accessory duct in an attempt to prove the presence of a true double gallbladder.

Cholecystectomy was performed and a pe-

FIG. 1. The double shadow of the gallbladder is well seen, as is also the very small hypoplastic kidney. Note the fine white line on both sides of the lower gallbladder shadow, especially well seen on the lateral aspect.

FIG. 2. Examination in the erect posture shows no communication between the two pouches, but again demonstrates the dye in the Rokitansky-Aschoff sinuses around the lower pouch and at the constricted waist of the gallbladder.

culiar gallbladder was encountered that contained no gallstones. The lower two-thirds of the organ had a uniformly greatly thickened wall measuring 1.5 cm. in thickness, and the cavity corresponded approximately in size to the lower shadow seen on the cholecystogram (about 2 by 4 cm.). At the upper end of the cavity, the lumen narrowed abruptly to a filiform size due to a narrow constriction, after which it again became widened into a small sac about 2 cm. in diameter, the walls of which were thin and had the appearance of a relatively normal gallbladder. This second sac then emptied into a short cystic duct, which entered a somewhat dilated common duct in the usual fashion. Only

FIG. 3. After a fat meal, there is demonstrated good contraction of the upper pouch, and the short cystic and the common duct are visualized. The Rokitansky-Aschoff sinuses around the lower pouch are much better visualized at this time since the intracystic pressure is increased.

FIG. 4. Another view after the fat meal from a slightly different projection, showing further contraction of the upper pouch and very good visualization of the Rokitansky-Aschoff sinuses in the mid-portion of the gallbladder in the region of the stricture.

one cystic duct was found and the gallbladder was apparently a single one with a narrow constriction dividing it into two segments (Fig. 6). The thickened lower portion of the gallbladder was rubbery in consistency, and considerable subserosal fat was evident. Just below the mucosal surface, there was a bile-stained thin layer running parallel to the surface in which a few tiny cystic spaces, about 1 mm. in diameter,

Fig. 5. Another cholecystogram on this patient shows both pouches more equally contracted and again demonstrates the dye in the Rokitansky-Aschoff sinuses.

were seen. This layer corresponded exactly to the one visualized in the cholecystogram.

Microscopic sections (Fig. 7 to 10) showed that the mucous membrane still looked relatively normal. Projecting downward from the surface epithelium were long crypts which passed through the subepithelial and muscle layers and formed tiny cystic spaces and duct-like ramifications in the connective tissue just external to the muscle layer. It seems inescapable that the presence of cholecystographic dye in these structures is what gave the peculiar extra shadow around the lumen of the gallbladder. The better visualization of this concentric ring when the gallbladder was contracted is what one would expect with herniations of the mucosa through the muscularis.

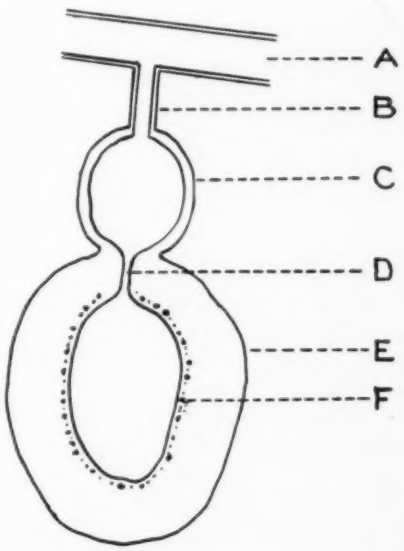


Fig. 6. A schematic drawing in longitudinal section of the operative and gross pathological findings. *A*, common duct; *B*, cystic duct; *C*, upper pouch of gallbladder; *D*, stricture of gallbladder; *E*, greatly thickened lower pouch of gallbladder; *F*, bile stained row of Rokitansky-Aschoff sinuses.

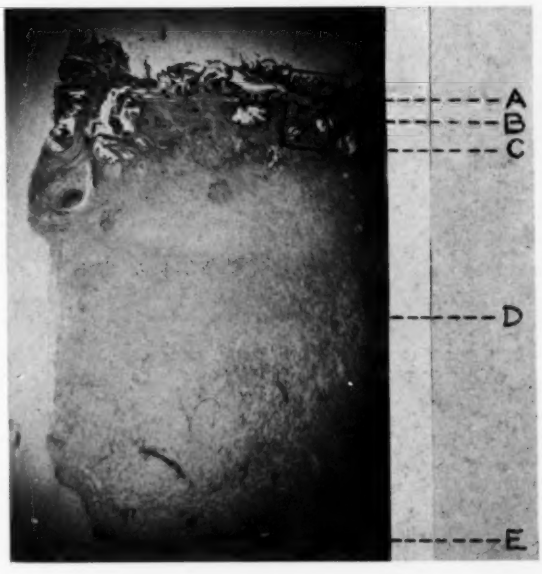


Fig. 7. Low power (5×) of microscopic section of wall of lower pouch of gallbladder. *A*, mucosa; *B*, muscular layer (small, dark bundles); *C*, Rokitansky-Aschoff sinuses in perimuscularis; *D*, greatly thickened perimuscularis; *E*, serosa.

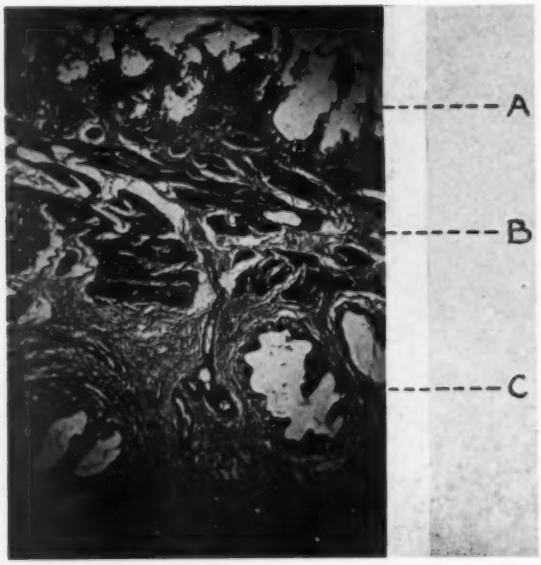
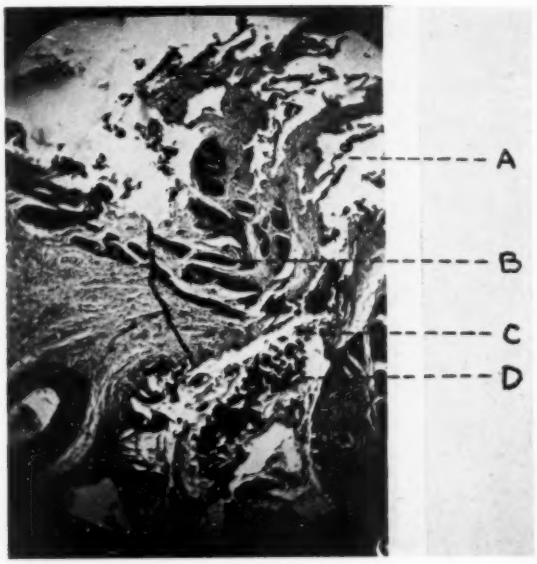


Fig. 8. Low power (60×) photomicrograph of the small rectangular segment marked in Figure 7.



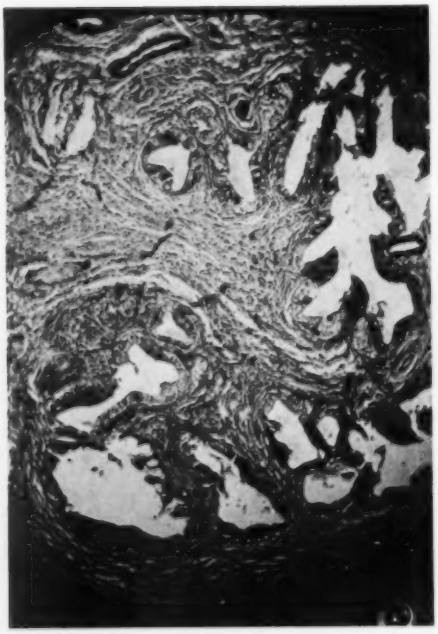


Fig. 10. This shows the branching sinuses in the perimuscularis. The muscle layer is above the field included in this view.

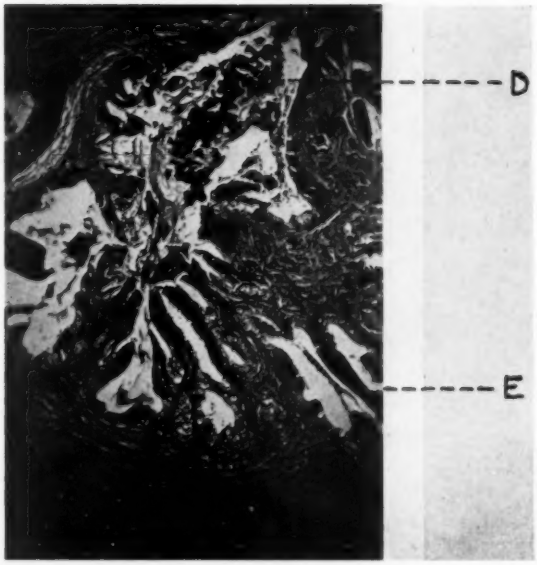


Fig. 9. Low power (60×) photomicrograph showing the actual penetration of the muscular layer by a branching Rokitansky-Aschoff sinus. The black granular material in the lumen is a clump of cholesterin crystals. The lower photomicrograph is a continuation of the upper since the entire sinus could not be included in a single field. *A*, mucosa; *B*, muscular layer; *C*, penetration of muscular layer by Rokitansky-Aschoff sinus; *D*, cholesterin crystals; *E*, terminal ramifications of the sinus in the perimuscularis.

The major portion of the increased thickness of the gallbladder was due to a marked thickening of the fibrous tissue layer between the thin muscular coat and the serosal surface. Numerous fat cells were present in this proliferated connective tissue matrix, and a few small foci of lymphocyte aggregations were present.

DISCUSSION

In a series of studies dealing with the morphology of the gallbladder, Halpert[2,3] clearly distinguishes the so-called "Rokitansky-Aschoff sinuses" from what he calls the "true Luschka ducts" as found in the gallbladder, and he calls attention to some historical confusion in the naming and recognition of these structures. Rokitansky in 1842 called attention to "hernia-like outpouchings of the gallbladder mucosa" toward the external layers of the gallbladder, and Aschoff in 1905 first described them in terms of modern histology, calling them "Luschka's ducts" and emphasizing their pathological significance especially in connection with biliary stasis in the gallbladder and with the formation of gallstones. It was soon pointed out that these structures were not the aberrant bile ducts discovered by Luschka in 1863 in the wall of the gallbladder.

According to Halpert, the normal human gallbladder has four layers: (1) the mucosa; (2) the muscularis; (3) the perimuscularis; and (4) the serosa. The mucosa consists of a single row of uniform columnar epithelium. It is thrown into very small folds that give a fine reticulated effect to the surface. The epithelium rests on a very thin layer of connective tissue called the subepithelium, which accommodates the rich capillary plexus of the mucosa. The human gallbladder has no submucosa. The muscularis is a very thin web of longitudinal, oblique and circular delicate muscle bundles, with a small amount of cellular connective tissue between them. The perimuscularis is a layer of connective tissue around the muscularis. It is denser just beneath the muscularis, and is looser, less cellular and contains some fat cells in the subserous portion. The serosa is found only on the peritoneal aspect of the viscus.

The healthy human gallbladder rarely shows the presence of Rokitansky-Aschoff sinuses.[2] If present at all, they are shallow. The name is applied to the deeper outpouchings or sinuses of the gallbladder mucosa which dip down into the muscularis or extend as finger-like processes through the muscular coat into the perimuscular layer.[3] It is thought that these are not proliferations, but are herniations into and through the interstices and delicate septa between the muscle bundles. Halpert feels that the muscularis of the healthy gallbladder under ordinary conditions is dense enough to prevent such outpouchings. When the gallbladder is pathologically involved, there occurs in it a more or less general loosening and weakening of the contractile elements with a widening of the intermuscular septa, under which circumstances extreme contractions which follow prolonged and repeated overdistentions of the viscus are most likely to play the leading part in the production of these herniations. The length, diameter and manner of penetration of the Rokitansky-Aschoff sinuses show infinite variations. The most distal portion or fundus may show a wider lumen if it penetrates into the perimuscularis, the narrower neck causing it to resemble a round-bottomed flask.

True Luschka ducts are fine duct-like structures lined with cuboidal epithelium and with lumina generally less than 0.3 mm. in diameter, that are found occasionally in the outermost layers of the gallbladder wall, usually on the hepatic surface of the viscus. They have a fibrous wall of their own with the histologic structure of intrahepatic bile ducts. They never communicate with the lumen of the gallbladder.

The gallbladders which show Rokitansky-Aschoff sinuses are usually thickened, owing to an infiltration of inflammatory cells in the subepithelial layer and the perimuscularis as well as connective tissue proliferation and some edema; in other words, evidence of chronic cholecystitis.

They may be found associated with gallstones. Sometimes, these crypts or sinuses undergo cystic dilatation, producing small macroscopically visible cysts, and the condition is then designated as chronic cystic cholecystitis.

In 1931, King and MacCallum[3] described a condition which they called cholecystitis glandularis proliferans, in which there was a marked localized or diffuse thickening of the gallbladder. The outstanding feature of the thickened area was a marked downgrowth of the epithelium through the subepithelial and muscular layers, invading the greatly thickened subperitoneal layer. The authors regard the process as a definite proliferation. They make no mention of any resemblance or possible relationship to Rokitansky-Aschoff sinuses. The fact that many of their cases showed only localized involvement with nodule formation would indicate that the process they were describing was not a phenomenon of evagination, but was actually a proliferative one. Nevertheless, the microscopic sections of both conditions show considerable resemblance, unless there is also a proliferation of smooth muscle elements around the crypts, in which case the condition would resemble a so-called "adenomyoma." These epithelial crypts were entirely orderly in arrangement and the cells were benign in appearance. When the condition was localized, the thickened nodule might project from either the mucosal (and would then be regarded as a papilloma) or the serosal surface. Some of their cases showed small macroscopic cysts, and then they were indistinguishable from cholecystitis cystica. The marked thickening of the involved areas was due in large part to extensive proliferation of connective tissue cells and to deposits of fat intermingled with the connective tissue. Collections of small round cells were also encountered. Many of these cases grossly were thought to be carcinoma of the gallbladder because of the marked thickening of the wall. Two of the latter were originally considered malignant even microscopically, but the subsequent benign clinical course made this diagnosis untenable. The patients all had signs and symptoms of chronic cholecystitis. The vast majority had gallstones at operation, and more than one-third had an acute inflammatory process superimposed. The condition was found in 9.5 per cent of 400 gallbladders, but the cases were somewhat selected, since a number were referred to the authors because of their interest in the condition. King and MacCallum make no mention of the results of cholecystography in this condition. They felt that the condition had been described previously many times under a variety of names: adenoma, polyp, cystadenoma, fibro-adenoma, adenomyoma, etc.

In the case being reported in this paper, it was felt that the stenotic stricture in the gallbladder was congenital, both from the nature of the abnormality, the relative youthfulness of the patient and the presence of a second congenital abnormality, a marked hypoplasia of the right kidney with the characteristic bud-like pelvis. The markedly thickened lower sac of the gallbladder apparently represents a chronic cholecystitis showing marked Rokitansky-Aschoff sinuses. The microscopic picture would also fit into the description of cholecystitis glandularis proliferans, and Halpert[4] finds it difficult to distinguish the two, and does not feel that the latter is a clearly defined entity, but rather a confusion of cases of chronic cholecystitis showing Rokitansky-Aschoff sinuses with cases of adenomyoma that may or may not be accompanied by chronic cholecystitis. It is impossible to tell whether absorptive and concentrating power was present in both sacs, or in the upper sac alone, in which event the concentrated dye may have merely settled into the lower sac by gravity. The fact, however, that the lower sac demonstrated good contractile power suggests that it probably also had concentrating function.

SUMMARY

1. Rokitansky-Aschoff sinuses of the gallbladder are discussed.

2. The confusing similarity of some cases of cholecystitis glandularis proliferans to Rokitansky-Aschoff sinuses is brought out.

3. When Rokitansky-Aschoff sinuses are visualized during cholecystography, a unique picture is produced, which seems to be characteristic.

4. Visualization is rare probably because gallbladders showing Rokitansky-Aschoff sinuses are diseased, and concentration is probably usually considerably impaired.

5. A case is reported in which visualization of Rokitansky-Aschoff sinuses during cholecystography occurred.

6. Of secondary interest in this case is a double gallbladder shadow produced by a stricture in the body of the gallbladder.

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MYOSITIS OSSIFICANS PROGRESSIVA IN HOMOZYGOTIC TWINS*

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WE HAVE had the opportunity of studying homozygotic twins in both of whom the rare condition, myositis ossificans progressiva, was present. These two cases are being presented because the condition has not been reported, previously, as occurring in twins. The occurrence of myositis ossificans progressiva in identical twins, although it does not definitely establish the fact, strongly suggests that the etiological factor in this disease is a genetic one.

MYOSITIS OSSIFICANS PROGRESSIVA

"Myositis ossificans progressiva" is a misnomer in that the pathologic condition which bears this name is neither a myositis nor an ossification of muscles. On the contrary, there is an ossification of the connective tissue about the muscles. This connective tissue is frequently attached to the bones or forms an articulation with the bone. Mair has suggested the more appropriate name of "fibrositis ossificans progressiva." There is usually an associated characteristic deformity of the metatarsals, metacarpals and phalanges, particularly of the great toes and thumbs, which resembles hereditary deforming osteochondrodystrophy.

A case of myositis ossificans was first described and recorded in the literature by Guy Patin in 1692. It was given its present name of myositis ossificans progressiva by von Dusch in 1868. Numerous cases have been reported since that time.

DISCUSSION

Many normal variants as well as many pathological conditions are gradually being established as inheritable entities. This presentation is not concerned with the numerous abnormalities of the nervous system, the hematopoietic system or the viscera in which heredity is justly presumed, or has been definitely proved to be an etiological factor. We are not particularly concerned with inheritable abnormalities of the muscles since myositis ossificans progressiva, as has already been pointed out, is really not a condition which is primary in the muscles but is rather an ossification of the connective tissues.

There are numerous abnormalities of the skeleton and adjoining soft tissues in which heredity has been definitely proved, i.e.,

Brachydactyly—middle phalanx short or fused to terminal phalanx.
Minor brachydactyly.
Polydactyly.
Arachnodactyly—unusually long bones associated with other somatic defects.
Absence of patella.
Syndactyly—web fingers.
Osteochondrodystrophies—achondroplasia, multiple exostoses, enchondromas, chondromas, chondrodysplasia, lipochondrodystrophy (gargoylism).
Sclerosing osteopathies—osteopoikilosis, osteopetrosis, melorrheostosis.
Osteogenesis imperfecta (certain types).
Osteitis deformans (possible hereditary factor).

Myositis ossificans progressiva is an abnormality characterized by skeletal anomalies, as illustrated elsewhere, and by the ossification of the connective tissues adjoining the bones. We believe this condition should be added to the above list of inheritable conditions. The presumptive evidence upon which this contention is based is the occurrence of this abnormality

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(with similar-appearing lesions) in homozygotic twins.

Other observers have recognized the possibility that myositis ossificans progressiva is an inherited condition. We believe that we have brought forth evidence to further substantiate this impression.

ETIOLOGY

The etiology of myositis ossificans progressiva is unknown. There have been numerous theories propounded regarding its cause. These will not be elaborated upon or even reviewed since we believe there is now sufficient evidence to establish the most probable cause as being an hereditary one. This impression has been based on the following evidence:

1. The occurrence of myositis ossificans progressiva in monozygotic twins (as reported in this presentation).
2. The occurrence of this rare condition in father and son as reported by Burton-Fanning and Vaughn. Gaster also reported the disease in a father and grandfather, as well as in three sons, all in the same family.

   Uehlinger stated that the disease is probably hereditary. He also stated that, etiologically, the traumatic, inflammatory, trophoneurotic and blastomatous theories could be rejected, that the disease was a true mutation of the mesenchyma.
3. The frequent association of deformities of the extremities in myositis ossificans progressiva which roentgenologically resemble osteochondrodystrophy, a recognized hereditary condition.

In a personal communication, Dr. R. R. Spencer, Director of the National Cancer Institute at Bethesda, Maryland, states:

> The fact that the disease [myositis ossificans progressiva] occurred in monozygotic twins does not establish it as genetic, for there are many factors other than genes that identical twins have in common.
>
> *The occurrence in monozygotic twins does, however, suggest genetic influence,* but the critical test is the comparison of a series of cases in monozygotic twins with another series of cases in dizygotic twins. Owing to the rarity of the disorder it is doubtful that such a comparison can ever be made.

CLINICAL MANIFESTATIONS

The condition is more frequent in males although it may occur in either sex.

It is first manifested in infancy or early childhood by a soft tissue swelling, usually beginning in the cervical or upper dorsal region. This is painful and tender. Redness and heat may be present, suggesting an acute process. The soft tissue swelling may spontaneously disappear or it may lose its acute manifestations, a firm mass remaining. Opacity due to ossification in this mass may be demonstrated roentgenologically. There is a progressive stiffness and limitation of motion of the neck, chest, back and later the extremities, particularly the shoulders. The dorsal aspect of the trunk is more frequently affected than the ventral aspect, and the upper half of the body more frequently than the lower half. The lower extremities are rarely affected.

Invalidism gradually develops with a resulting atrophy of disuse of the muscles. The patient becomes thin and weak.

The process is spontaneously arrested early in the third decade of life. Apparently it is related to the period of physiologic growth. The cases usually terminate fatally in the third or fourth decade due to intercurrent infections. The respiratory embarrassment is probably a contributing factor to the intercurrent infection.

There are usually associated congenital anomalies of the thumbs and great toes. The appearance is that of a microdactylia and it is due to absence or shortening of some of the phalanges and, frequently, fusion of the phalanges. There are also deformities of the proximal ends of the phalanges and distal ends of the metatarsals.

ROENTGENOLOGICAL MANIFESTATIONS

There is progressive ossification of muscle

sheaths, tendons, and intervening connective tissue.

Irregular bands of ossification are found in various portions of the body. The cervical region, particularly the sternocleidomastoid area is usually involved. The ribs and scapular areas, especially the connective tissues about the axillary muscles, are often affected. The ligaments of the spine usually contain extensive ossification. Ossification is present about the pelvis, particularly in the region of the hip joints and about the muscles of the thighs.

False joints (synostoses) may be formed with the ribs, spine, shoulder girdles, or about the hips. The osseous bands may result in bony ankylosis.

There is apicocaudal progression of the disease. Scoliosis is frequent. There is deformity of the thorax due to fixation of the ribs. Exostoses may project from the cortices of the long bones of the extremities. There is hallux valgus due to defective ossification about the metatarsophalangeal joints of both great toes (this resembles hereditary osteochondrodystrophy). The phalanges of the toes, particularly the great toes, and the fingers, especially the thumbs, are frequently fused and maldeveloped, resulting in microdactylia.

FIG. 1. Identical twins, C. M. and M. M. Note identical appearance, similar eyes, hair and features. The osseous structures and blood types are identical.

PATHOLOGY

Microscopic examination of a mass of bony structure from soft tissues of the back in one of our cases was reported as quite normal bone. The microscopic findings reported by various observers are almost as varied as the number of pathologists reporting. This wide variety of descriptions is probably due to a different stage of the disease existing at the time the particular examination was made.

CASE HISTORIES OF THE TWINS M. M. AND C. M. (FIG. 1)

M. M. was first seen in the clinic of the Woman's College Hospital in November, 1933, at the age of ten years. The chief complaint

was "stiff neck." It was also noted at that time that there was "soreness in the joints." The referring physician had advised admission for tonsillectomy and adenoidectomy since the patient was said to have had "attacks of arthritis" for three months. Accordingly the child was admitted to the hospital in January, 1934, at which time a tonsillectomy and adenoidectomy were performed. In the history, it was noted that there was constant stiffness in the region of the cervical vertebrae.

Past medical history included pneumonia, mastoiditis and measles before three years of age. A mastoidectomy had been performed when the child was two years old.

Physical examination included the observation that the patient had a fixed stare and that there was spasticity of all the extremities and the vertebrae. The fingers were held in a position of extension and the child held the right hand with the left. She could not sit upright but had to be propped up.

C. M. was referred for tonsillectomy and adenoidectomy to the same hospital in May, 1934, for "arthritis of the cervical vertebrae since July, 1930." There was a history of numerous colds with frequent swelling of the cervical glands.

Past medical history included only measles at six years.

Physical examination noted a thin, pale child of eleven years of age. The neck was stiff and the anterior cervical glands were enlarged. The back was stiff and there was a curvature to the left in the lumbar region. Bony sharp prominences were noted protruding from below the angles of the scapulae. The patient was unable to raise her arms to a right angle. The left phalangeometatarsal joint was enlarged and stiff and the left great toe was short.

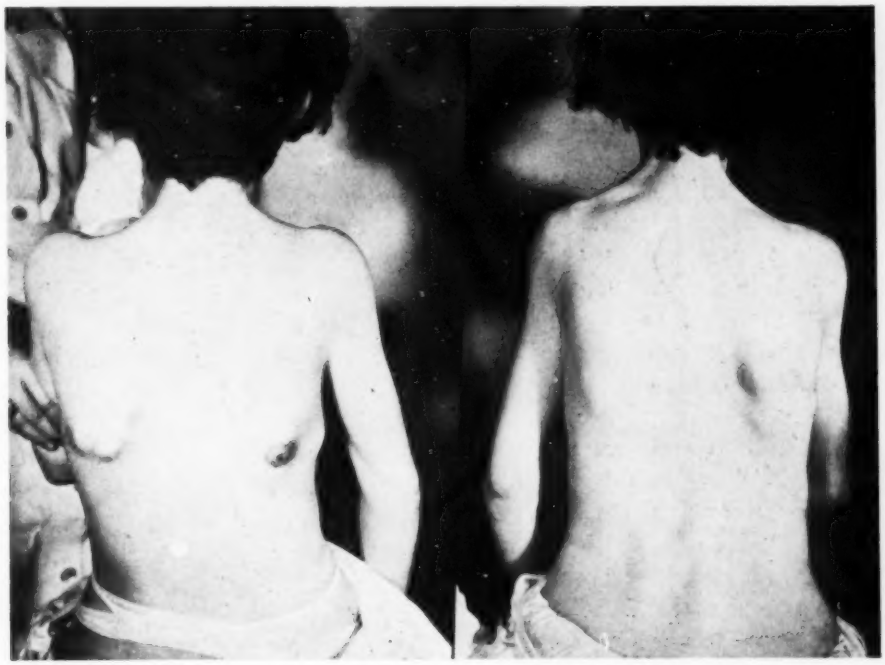

Fig. 2. Posterior view of twins. Deformity of back due to ossification in the soft tissues.

Birth and Family History of M. M. and C. M. Delivery normal. Both children weighed between 3 and 4 pounds at birth. They sat up at approximately eight months and walked at about eighteen months of age. Four brothers living and well; three sisters living and well. No siblings dead; no miscarriages.

No family history of any mental disease, congenital anomalies or diseases similar to this one. Maternal grandparents died in their eighties and paternal grandparents were both in their late seventies at the time of their deaths.

Comparison of Roentgenologic Picture and Follow-up on Twins

Five years after the hospital admission of the second twin (C. M.) both girls were

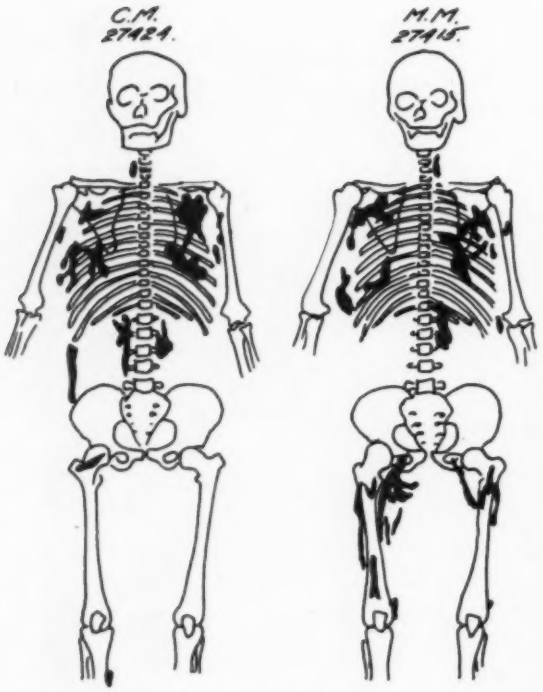

FIG. 3. Chart showing distribution of ossification the soft tissues (myositis ossificans progressiva).

referred to the department of radiology for study. The results of the roentgenographic examination are recorded schematically in Figure 3. In both there was ossification posteriorly in the cervical region (Fig. 4). From the histories it seems obvious that

FIG. 5. Roentgenogram of M. M. demonstrating ossification of the soft tissues of the back.

the disease in these cases, as in the typical cases recorded in the literature, became manifest first in the connective tissues lying in relation to the cervical muscles. In both girls abnormal ossification was seen to be most extensive in the subcutaneous tissues of the back (Fig. 2 and 5). M. M. showed much more extensive ossification about the

FIG. 4. Roentgenogram of the cervical region. There is ossification in the soft tissues posteriorly. The disease is usually first manifested in this region. Note anomalies of the cervical spine (Klippel-Feil syndrome).

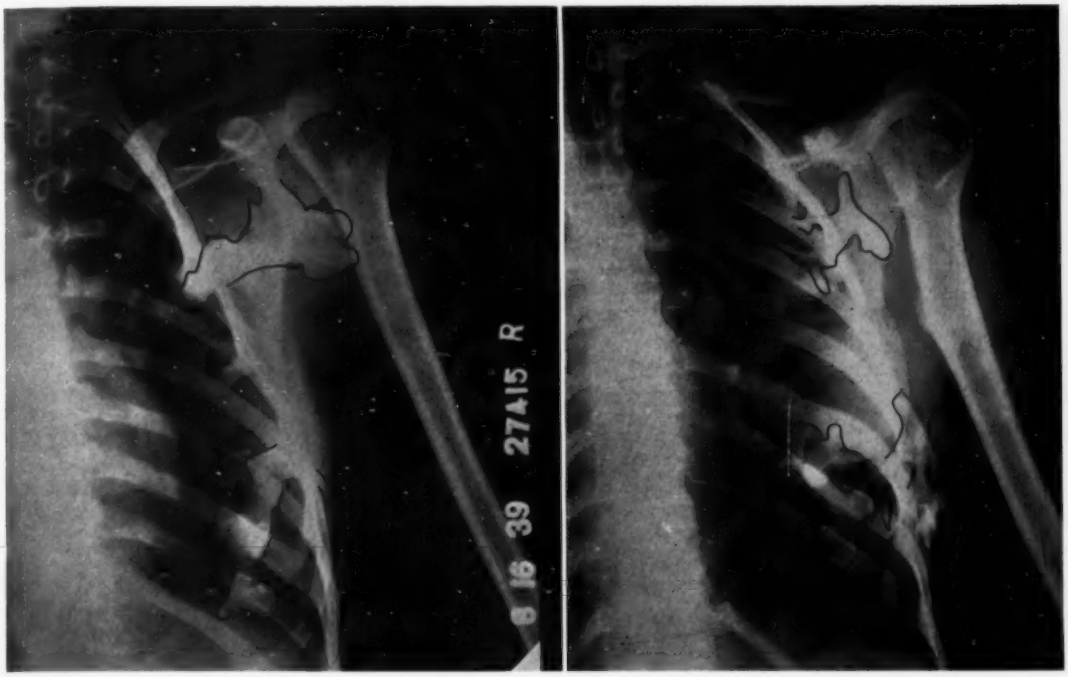

Fig. 6. Right thoraces and shoulders of identical twins, C. M., and M. M. Note similarity of skeletal structures roughly similar patterns of ossification in the soft tissues.

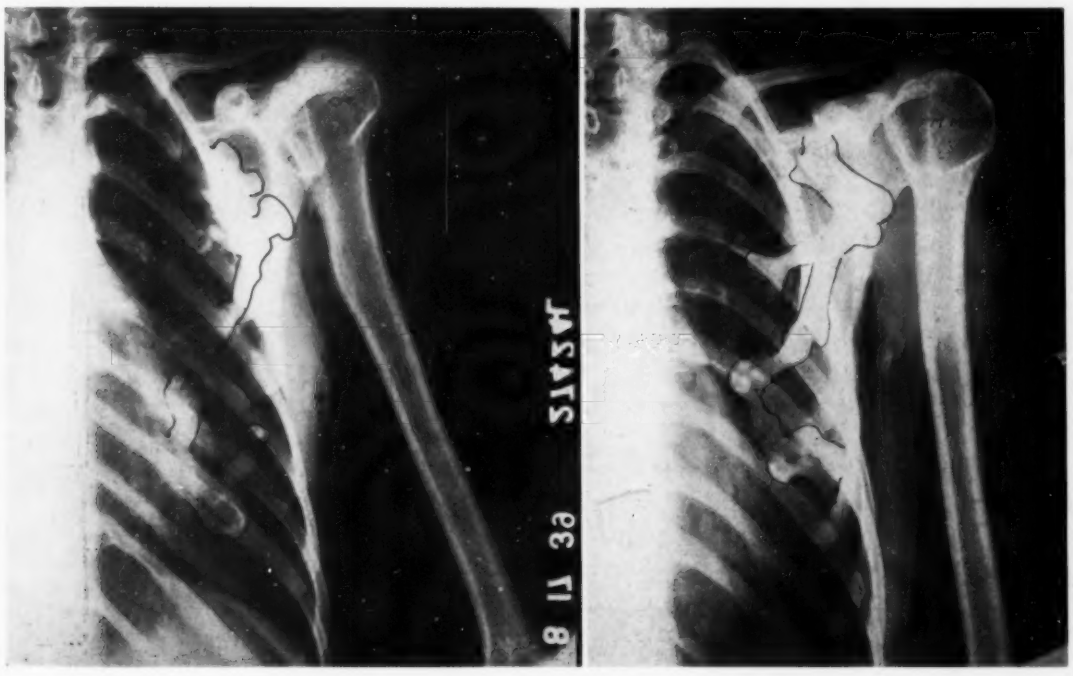

Fig. 7. Left thoraces and shoulders of identical twins, C. M., and M. M.

hip joints and upper femora than did C. M. (Fig. 8). In fact, for the past three years, M. M. has been unable to walk because of the immobility and fixation of the hip joints which has resulted from the abnormal deposition of bone in these areas. C. M. is still ambulant. As seen in Figure 8, there is deformity of the neck of the femur in C. M.

FIG. 8. Left hips of C. M. and M. M. There is deformity of the neck of the femur in C. M. resembling that seen in hereditary deforming osteochondrodystrophy. There is extensive ossification of the soft tissues in M. M.

which resembles that seen in hereditary deforming osteochondrodystrophy. Figure 9 shows fusion of the phalanges in the great toes of both patients. There is hallux valgus with deformities of the distal ends of the first metatarsal bones

CRITERIA FOR ESTABLISHING THE IDENTITY OF HOMOZYGOTIC TWINS

Identical (homozygotic) twins are the product of one fertilized egg which has divided. The two halves of this egg, barring deformities or changes incident to environment or acquired diseases, must be identical. The criteria, now established, for identifying twins include:

(1) Blood group—the same.
(2) Handedness—the same (although this may be altered by training).
(3) Eyes—the same color and pattern.
(4) Hair—the same color, form, and the same whorl.*
(5) Finger prints and foot prints—the same general patterns although not identical finger prints.
(6) Identical skeletal development* and patterns of ossification† of the costal cartilages as demonstrated on roentgenograms.

The twins, M. M. and C. M., fulfill these criteria. Their blood type is B and they are both Rh positive. Figure 6, showing the right thoraces and shoulders of the twins, demonstrates the similarity of the skeletal structures. A roughly similar pattern of ossification is demonstrable in the soft tissues.

* The handedness, hair whorls, and skeletal structures are the same in homozygotic twins except in cases of reverse or mirror-imaging in which cases these characteristics are reversed.

† The authors, in another paper in this issue of the JOURNAL, discuss their reasons for including this among the criteria for establishing the identity of homozygotic twins. (This publication is entitled "Genetic Influence on Osseous Development with Particular Reference to the Deposition of Calcium in the Costal Cartilages.")

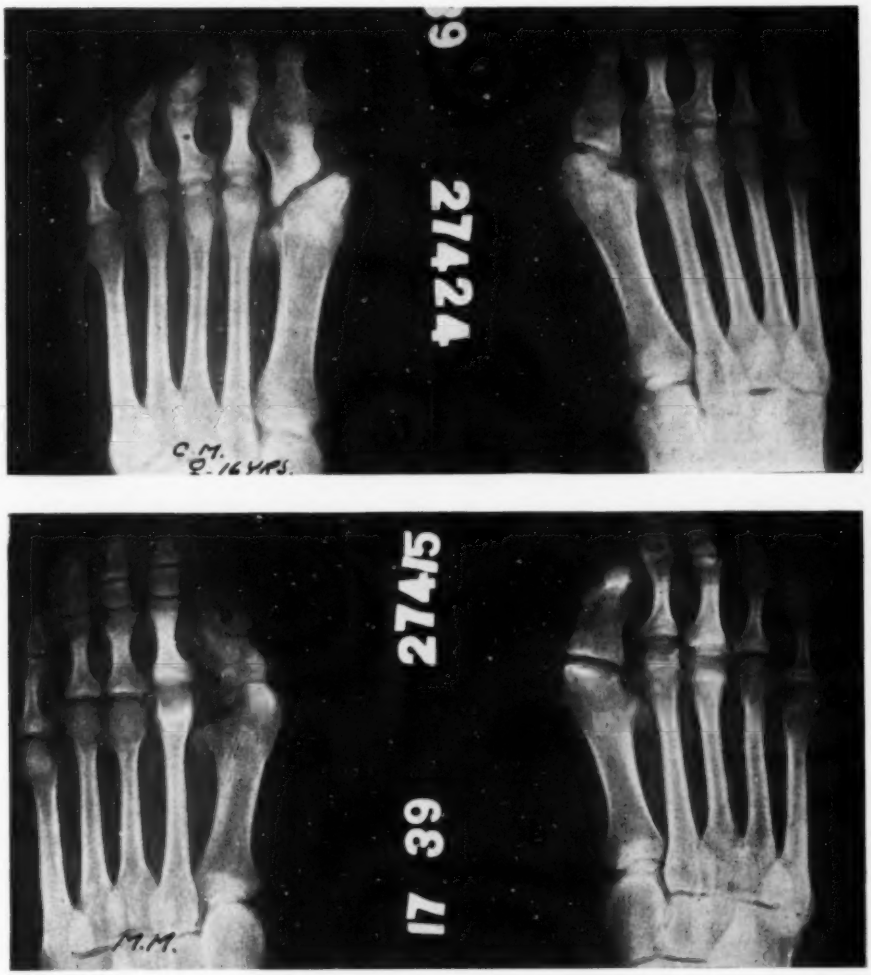

Fig. 9. Roentgenograms demonstrating similar deformities of the feet of the identical twins, C. M. and M. M. These changes consist of deformities of the great toes of both feet of both twins with fusion of the phalanges, hallux valgus and deformities of the distal end of the first metatarsals. Similar changes are also usually observed in the hands. They are quite characteristic of myositis ossificans progressiva and closely resemble the changes seen in hereditary deforming osteochondrodystrophy.

SUMMARY AND CONCLUSIONS

1. Myositis ossificans progressiva is a pathologic condition characterized by ossification of the connective tissues about the muscles.

2. The authors have observed the condition in identical twins.

3. Hitherto, the etiology of myositis ossificans progressiva has been questionable.

4. It is believed that its occurrence in homozygotic twins indicates that myositis ossificans progressiva is genetic in origin.

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GENETIC INFLUENCE ON OSSEOUS DEVELOPMENT WITH PARTICULAR REFERENCE TO THE DEPOSITION OF CALCIUM IN THE COSTAL CARTILAGES*

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THE influence of heredity as an all important factor in the acquisition of many abnormalities of the skeletal system and adjoining soft tissues is well known. It is not so well known that the ossification which occurs normally in the costal cartilages is hereditarily determined. That this is true seems to have been proved by the occurrence of similar ossification patterns in the corresponding costal cartilages of identical twins.

HEREDITY

A brief discussion of the fundamental concepts of heredity may help to clarify the data and conclusions which are to follow.

The male reproductive cell (spermatozoon) containing twenty-four chromosomes combines with a female reproductive cell (ovum) containing twenty-four chromosomes. The chromosomes are the dark staining microscopic material in the nucleus of the cells. These chromosomes have a definite size and shape. The chromosomes are made up of smaller definite entities which are called *genes*. To these genes are attributed the hereditary determiners which establish the exact arrangement of the somatic cells of the new organism.

The somatic cells of the body all contain two sets of twenty-four chromosomes each or forty-eight. Half of these are derived from the sperm and half from the ovum. The characteristics of the body depend on the hereditary characteristics transmitted through the genes making up the chromosomes. When the sperm and ovum, each containing twenty-four chromosomes, unite there results a fertilized ovum (zygote) containing forty-eight chromosomes or body determiners. These determine to the minutest detail how the body or somatic cells will look and how they will act. This means not only the appearance of the features and habitus but the roentgenological appearance of the finest details of the arrangement of the somatic cells (particularly of the osseous structures with which we are chiefly concerned in this presentation).

If, shortly after it begins to grow, a fertilized egg (zygote) splits in half to form two individuals, each will have exactly the same hereditary factors and *identical twins* will be the result. Since they are derived from the same fertilized egg (zygote) they are called *homozygotic* twins. If the division takes place after the embryo has begun to differentiate, the twins are opposite each other. Thus the right side of one homozygotic twin corresponds to the left side of the other twin. This is known as *reversal* or *mirror-imaging*. One twin is usually right handed, the other is left handed. The hair whorls are in opposite directions. The pattern of ossification of one side corresponds to the opposite side in the other twin.

The offspring contains the characteristics transmitted through the genes of the two parents and these go on through succeeding generations unchanged except for mutations. Mutations are alterations of the genes by factors which are poorly understood. Cosmic rays have been sug-

* Presented before the Second Inter-American Congress of Radiology, Havana, Cuba, Nov. 17–22, 1946.

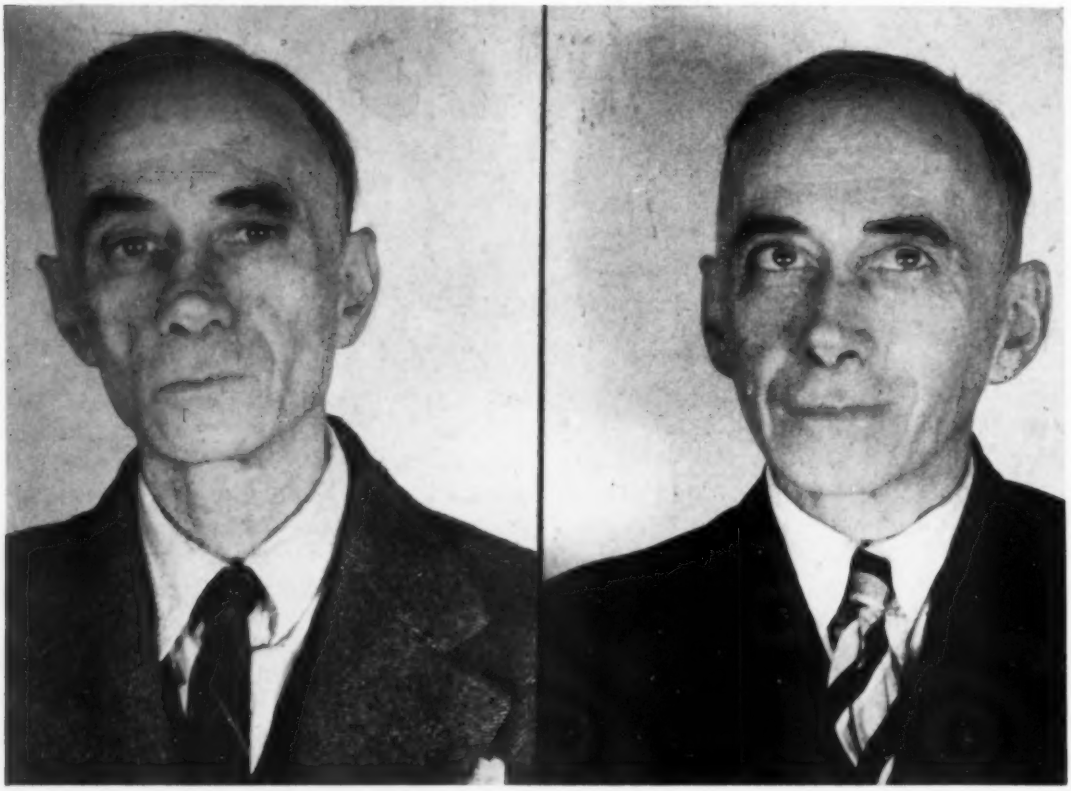

FIG. 1. Identical twins A. B. and J. B., aged sixty-two years.

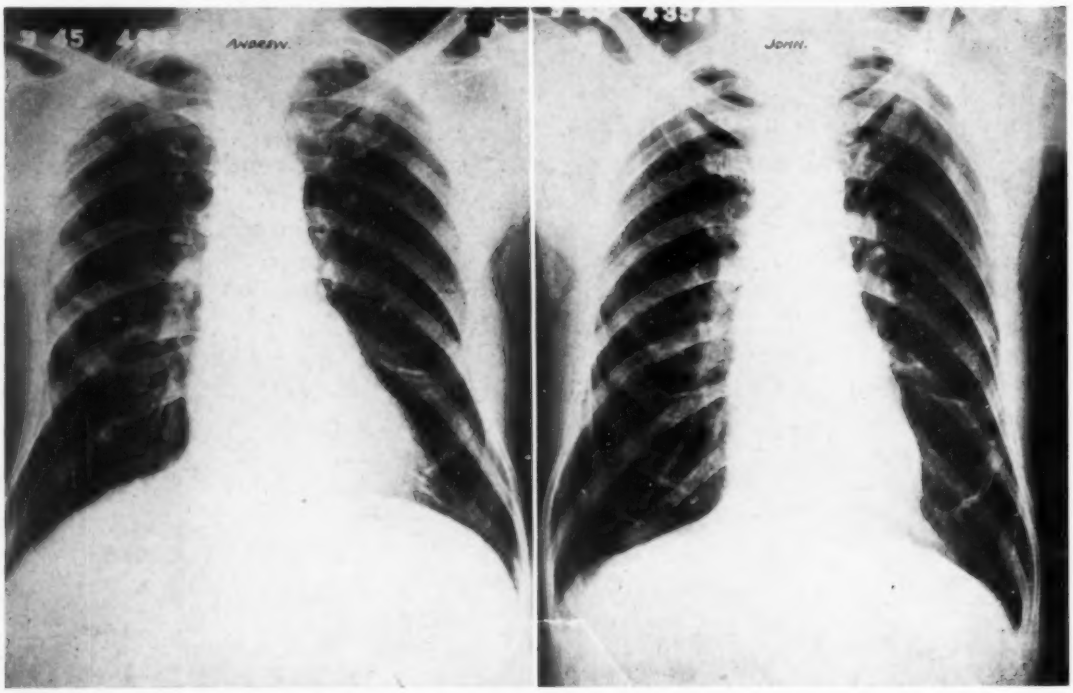

FIG. 2. Roentgenograms of the chests of identical twins A. B. and J. B. Note similar general contour of the ribs, the same patterns and degree of ossification of the costal cartilages.

gested as a possible cause of these changes (Muller). Malformations in rat embryos have been produced by Warkany and Nelson as the result of induced vitamin B deficiency. Gordon and Sang were able to prevent mutation in fruit flies following exposure to roentgen rays by the administration of niacin. These changes of the genes remain permanently and are carried through succeeding generations. Some of these mutations result in beneficial changes in the offspring and some of the effects are undesirable. The undesirable mutations are considered pathological. The beneficial changes as viewed over a long period constitute evolution or progress of the race.

Identical (homozygotic) twins are the product of one fertilized egg which has divided. The two halves of this egg, barring deformities or changes incident to environment or acquired diseases, must be identical. The present criteria for identifying twins are:

(1) Blood group—the same.

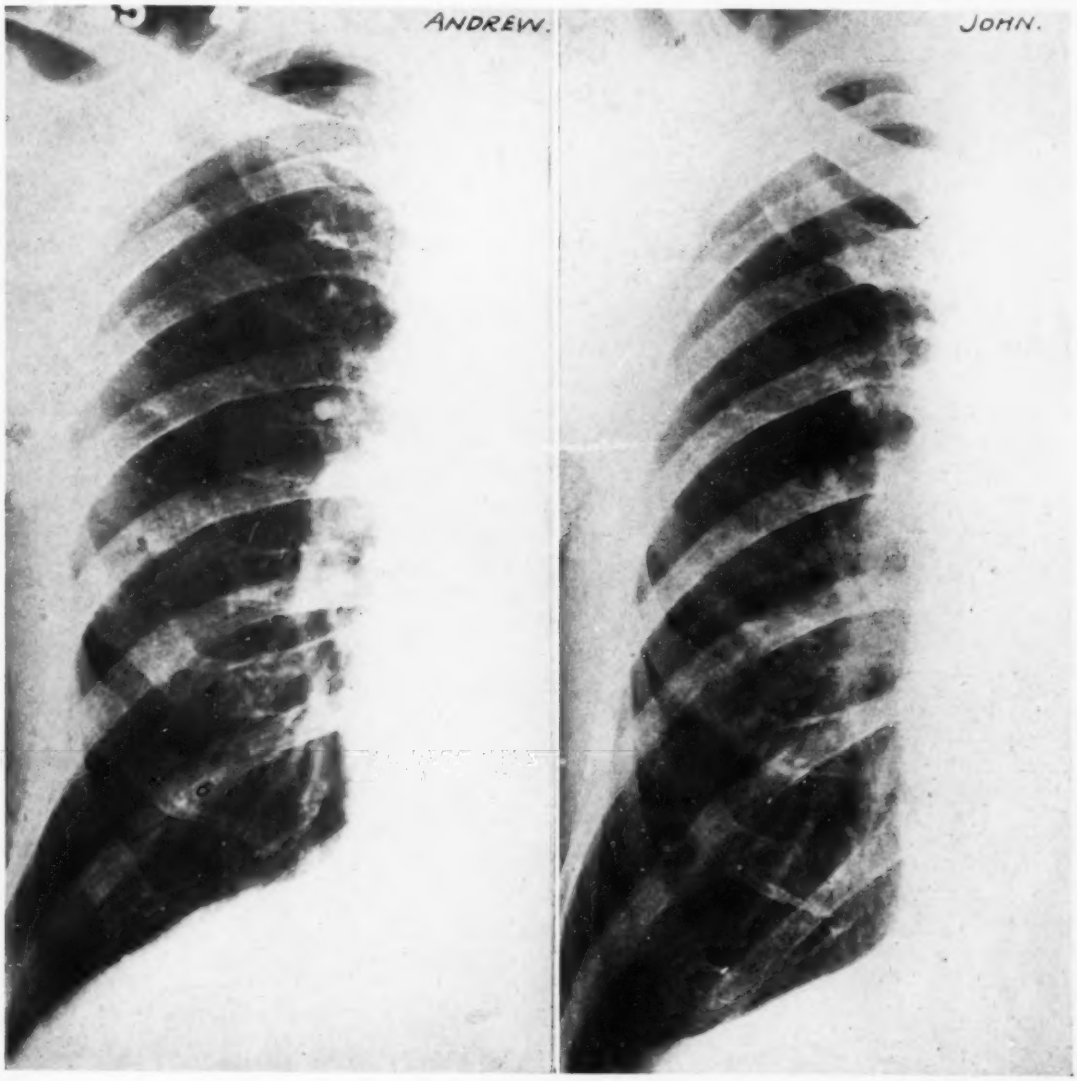

Fig. 3. Enlarged section of the roentgenograms of the right sides of the chests of identical twins, A. B. and J. B. to demonstrate similar patterns of ossification of the costal cartilages.

(2) Handedness—the same although this may be altered by training.
(3) Eyes—the same color and pattern.
(4) Hair—the same color, form, and the same whorl.

The handedness, hair whorls, and skeletal structures are the same in homozygotic twins except in cases of reversal or mirror-imaging in which case these characteristics are reversed.

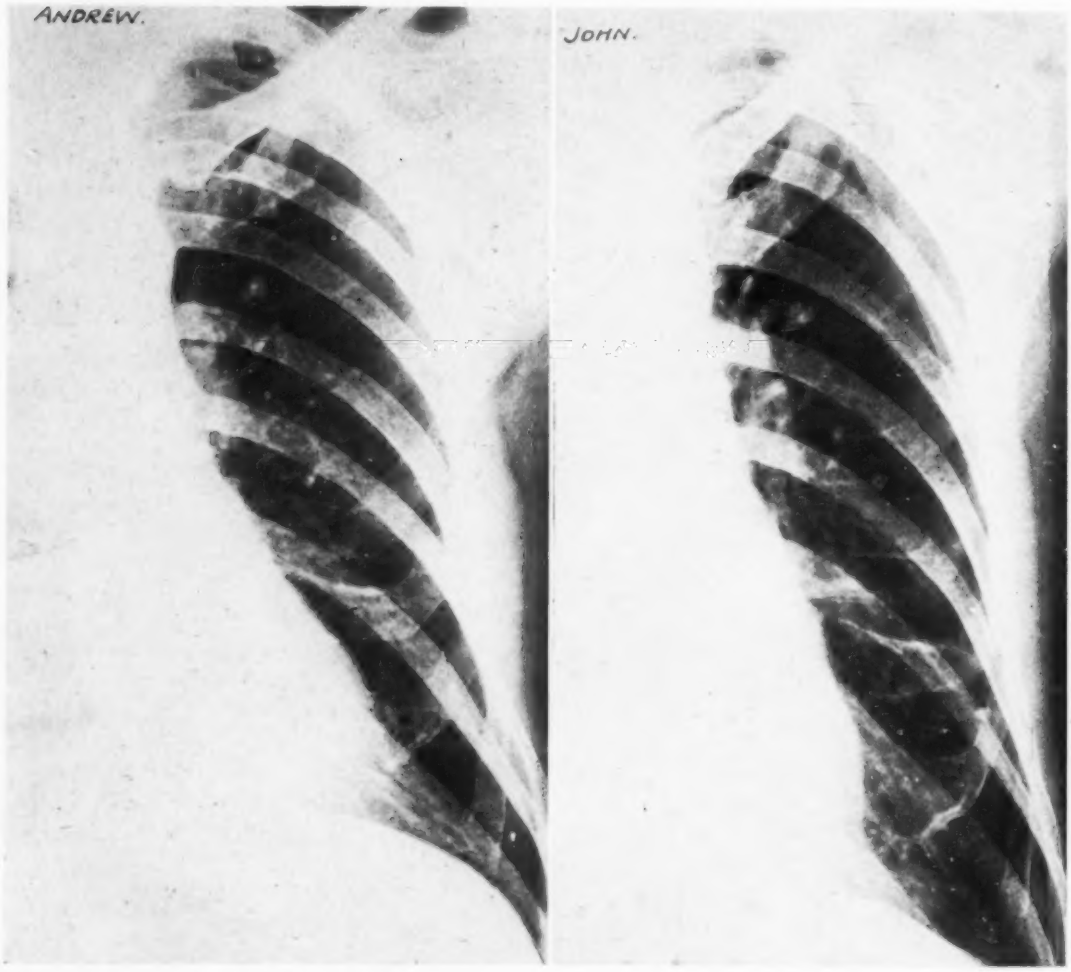

FIG. 4. Enlarged section of the roentgenograms of the left sides of the chests of identical twins A. B. and J. B. to demonstrate similar patterns of ossification of the costal cartilages.

(5) Finger prints and foot prints—the same general patterns although not identical fingerprints.

To these we would like to add a more accurate and precise method of establishing the identity of twins, i.e.,

(6) Identical skeletal development and patterns of ossification of the costal cartilages as demonstrated on roentgenograms.

GENETIC INFLUENCE IN OSSEOUS DEVELOPMENT

The size, shape and contour of the skeletal system is predetermined by the genes. Even the most minute detail of ossification is under the direct influence of the genes. This fact is evident only when a close comparison of the roentgenograms of each of the respective bones of identical twins is

Fig. 5. Identical twins M. S. and A. S., aged fifty-eight years. Roentgenograms of the right lower chest and lumbar spine. Note similar patterns of ossification of the costal cartilages, identical structures of the ribs of both as to size, shape and thickness of cortex. Note the similar shapes, size and directions of the transverse processes of the lumbar vertebrae of the twins.

Fig. 6. Identical twins E. B. and E. S., aged seventy years.

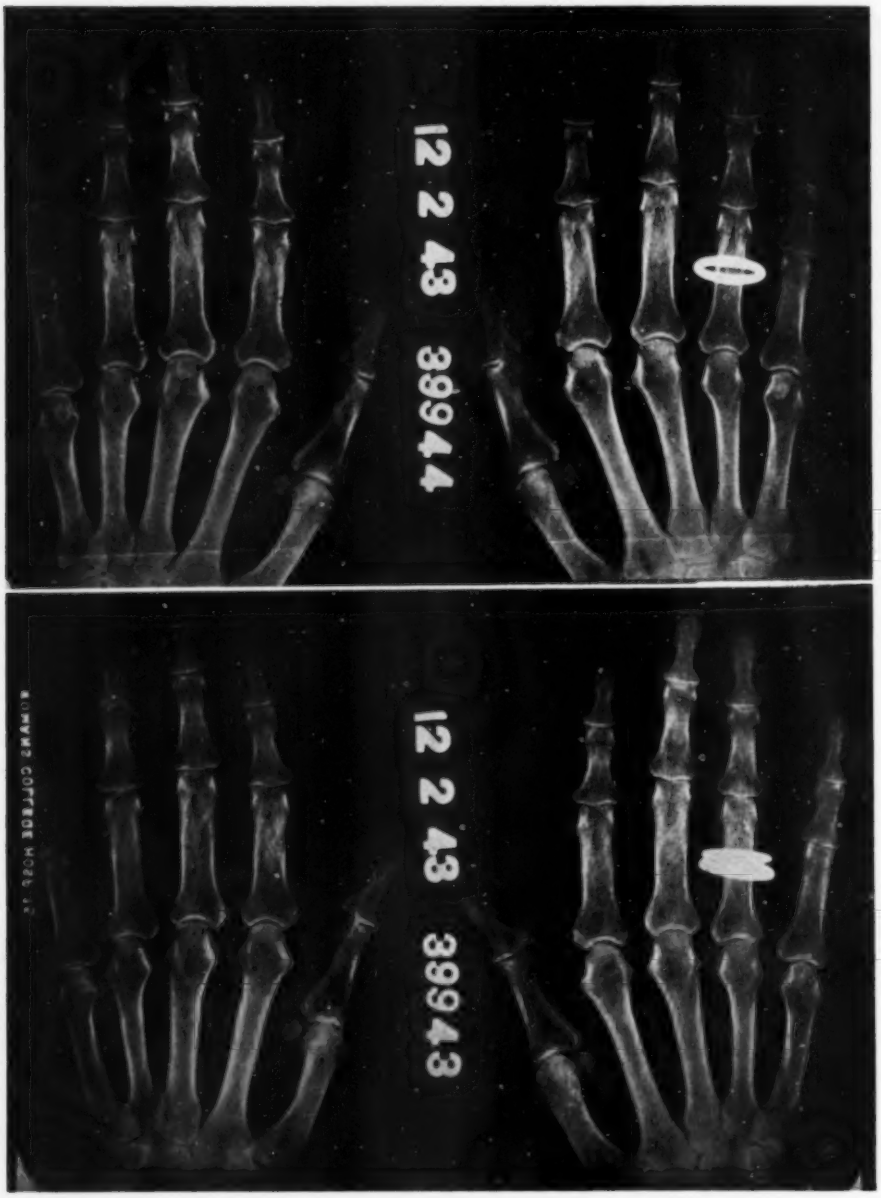

FIG. 7. Roentgenograms of the hands of identical twins E. B. and E. S. Note similarity of the general shape of skeletal structures and the fine bony detail, even to the identity of many of the trabeculations.

made. By such a comparison we will seek to establish the following facts or premises that:

1. The smallest detail of the bony structures of the skeleton is directly influenced by the genes as evidenced by a close comparison of the skeletal structures of identical twins, and that
2. This close similarity as observed on the roentgenogram may be utilized to identify homozygotic twins. In fact, it may prove to be our most accurate criterion in differentiating homozygotic from dizygotic twins.
3. The ossification of the costal cartilages is under the direct influence of the genes rather than the result of any recent or acquired influence as evidenced by the almost exactly similar

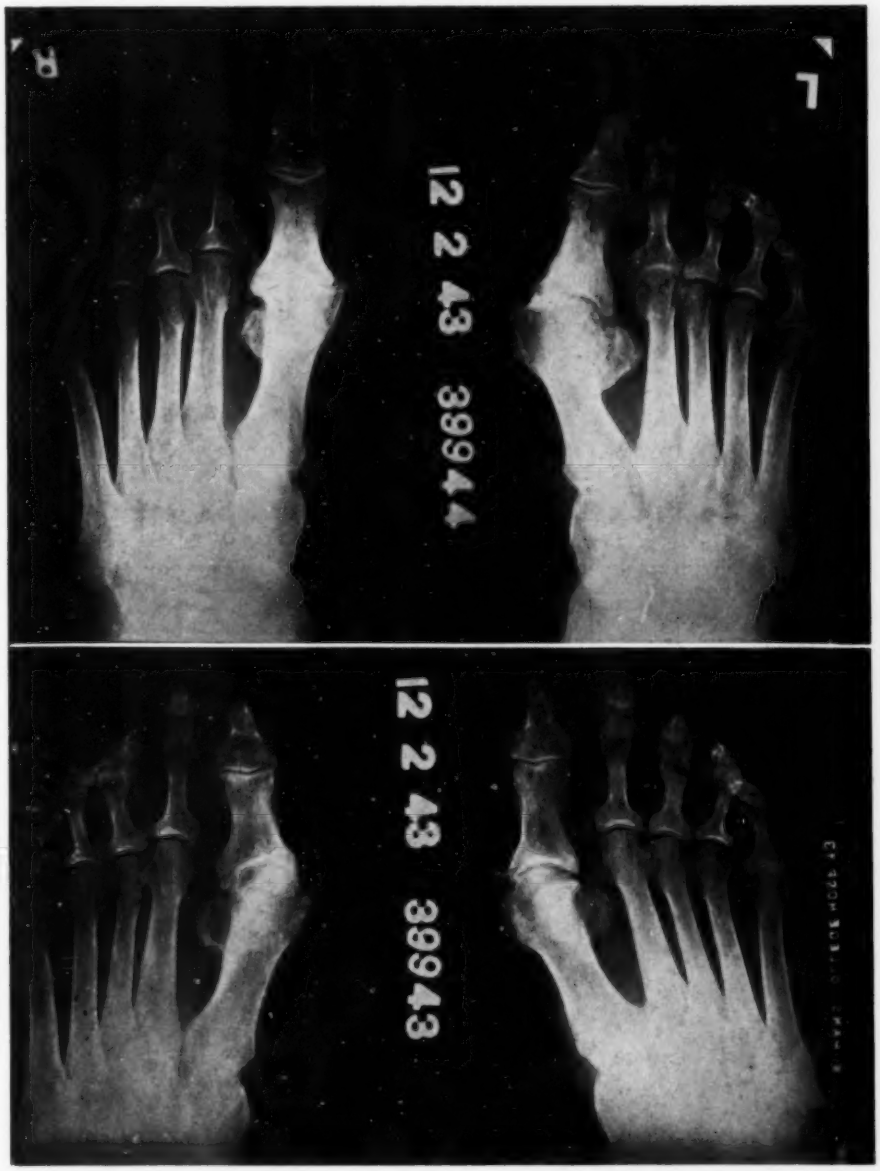

Fig. 8. Roentgenograms of the feet of identical twins E. B. and E. S. Note the similarity of the skeletal structures and similar but not identical degenerative changes of the joints.

patterns of ossification taken in each respective costal cartilage of identical twins.

The third observation is original. Similar observations to one and two were previously made by Rigler and the literature thoroughly reviewed in his study of twins and triplets.

There is exact similarity in the detailed ossification of the costal cartilages as well as in the fine bone detail. The shape of the ribs, the size, shape, and angulation of the transverse processes as well as the details in other skeletal structures have offered striking likenesses as observed by us in making extensive roentgenological studies of many identical twins. In identical twins in which there is a reversal or mirror-imaging, the skeletal structures and costal cartilages of the one side of one twin are identical to the corresponding structures of the opposite side of the other twin.

FIG. 9. Identical twins B. M. and M. M., aged twenty-seven years. There is mirror-imaging or reversal in these homozygotic twins as was demonstrated on the roentgenograms.

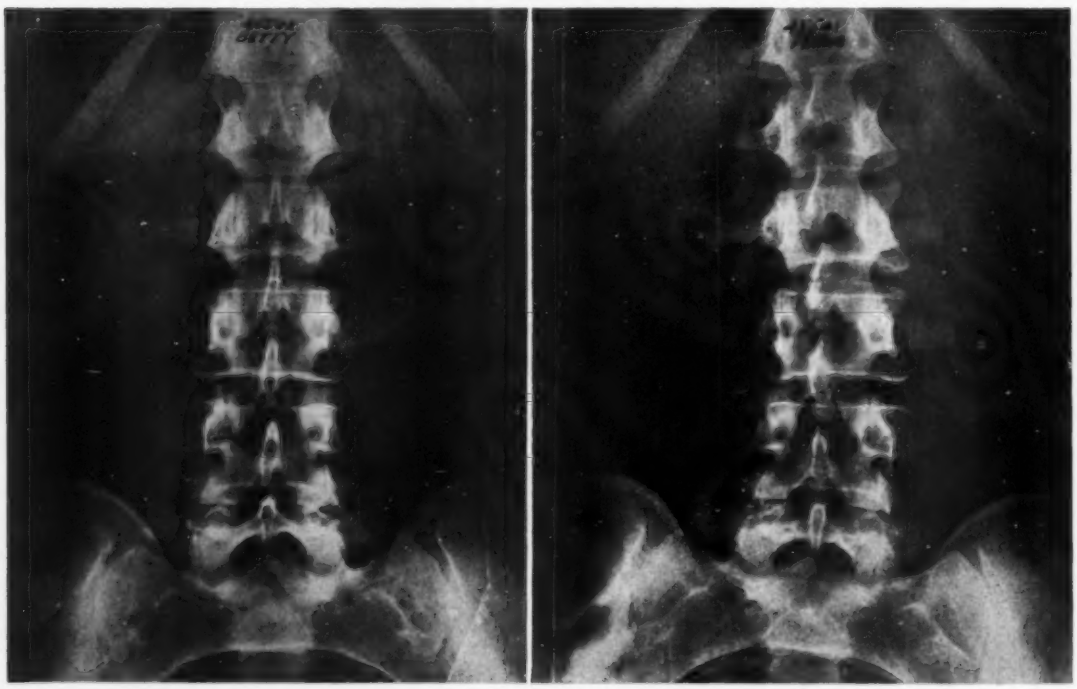

FIG. 10. Roentgenograms of the lumbosacral spines of identical twins B. M., and M. M. Note (1) that there are six lumbar vertebrae; (2) that there is a spina bifida occulta of the first sacral segment in each twin with the direction oppposite in the two twins; (3) that the transverse processes of the lumbar vertebrae on the one side of B. M. correspond to those of the opposite of M. M. in size, shape, length and direction; (4) that the shape of the crest of the ilium of the left side of B. M. is exactly similar to the crest of the ilium of the right side of M. M., and vice versa.

OSSIFICATION OF THE COSTAL CARTILAGES

There are few structures in the human body which have been the source of greater curiosity or more futile conjecture than the costal cartilages. This is probably due to the fact that the chest is the most frequently roentgenographed part of the body and the bizarre patterns of ossification seen in the costal cartilages are often the most striking feature in the roentgenogram.

Ossification progresses in a cephalocaudal direction, usually commencing in the first rib. The center of the cartilage first becomes ossified and later the costal and sternal ends.

These areas of ossification begin in the second decade and become more extensive as age advances. Isolated instances of very marked ossification at an early age have been observed. The cause or significance of this ossification has never been understood. It has been the source of many speculations and considerable investigation. Köhler made extensive observations and attempted to correlate the amount of ossification in the costal cartilages with arteriosclerosis. Ernst, in 1929, reported his observations. Rist, Gally and Trocmé also reported upon the subject in 1928. There are numerous other references to this phenomenon in the literature. Attempts have been made to correlate the degree of ossification in the costal cartilages with (1) susceptibility or resistance to tuberculosis; (2) states of nutrition (it is believed by some observers that ossification occurs at an early age in individuals suffering privations); (3) variations in the mineral metabolism; and (4) endocrine dyscrasias.

We believe that all of these have been erroneous. It was observed by one of us (M. F. V.) several years ago that the pattern of the ossification of the costal cartilages in a pair of identical twins was almost exactly the same. Thus the pattern in the first costal cartilage on the left side of twin A was similar to the ossification in the first costal cartilage on the left side of the twin B. This similarity obtained in both the amount of ossification and the arrangement.

Since that time we have had the opportunity to confirm these observations by comparing numerous sets of homozygotic twins. We have concluded that since an almost identical pattern or design of ossification occurs in the corresponding cartilages of identical twins, the pattern taken must be transmitted directly by the genes rather than be subject to any acquired factor or to any metabolic, nutritional or infectious influence. Since this has been uniformly true in all sets of identical twins which we have roentgenographed we believe that it constitutes one of our most accurate criteria for identifying homozygotic twins. Since it is such a consistent observation we believe that the ossification design in the costal cartilages is inherited through the genes rather than being the result of a mutation of the genes of a particular ovum before its division.

These observations have seemed to:

a. Establish the genetic influence as the main factor in the ossification of the costal cartilages.
b. Offer an easy criterion to aid in identification of homozygotic twins, and
c. Suggest the pathological insignificance of ossification of the costal cartilages.

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AN ANATOMICAL CLASSIFICATION OF CANCER OF THE LARYNX FOR USE IN RADIATION THERAPY*

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THE purpose of this paper is to present an anatomical classification of the clinical stages of cancer of the larynx which has been found to be of value in the prognosis of these cases. It contains no correlation with the microscopic findings but is concerned exclusively with the extent of the lesion at the time of the first complete examination.

One of the principal purposes for this type of classification is to re-emphasize to radiologists that "intrinsic" and "extrinsic" groupings have little importance in the prognosis of these individuals who are treated by means of radiation. "Intrinsic" and "extrinsic" as pointed out by Jackson and Jackson are all-important to the laryngeal surgeon, for, obviously, any lesion that begins or extends beyond the confines of the larynx cannot be cured by laryngectomy. However, from the radiological point of view, in an early lesion of the superior aspect of the aryepiglottic fold one can expect as good a result from irradiation as a similar sized lesion on the true cord. It is the extent of the lesion that is the most important prognostic finding, and not the location. This is not an attempt to decry the laryngologist's approach to the problem, but to point out that the radiologist has a slightly different outlook due to a lack of surgical limitations in his methods of treatment.

The classification that we feel meets most of the needs of the radiologist is shown in Chart 1. As is noted in this chart, the major portions of the larynx are located by name in the usual anatomical positions so that the precise extent of the lesion can be told, and thereby its exact stage. The terms "extrinsic" and "intrinsic" are retained because of their importance to the laryngologist and their widespread usage. A lesion confined to the right true cord would be termed "Intrinsic Stage I." If a lesion involved the left false cord and the left aryepiglottic fold, it would be called "Extrinsic Stage II" because those are immediately adjacent areas and one is outside the actual larynx.

To follow this classification it is necessary for the patient to have a complete examination of the larynx with direct visualization of the structures by means of the laryngoscope, and an adequate biopsy made. This should be supplemented by soft tissue roentgenograms of the neck. The laryngologist must describe the lesion in terms of the extent of structural involvement, paying particular attention to distinguishing between neoplasm and inflammatory reaction. Following this thorough direct examination and the return of the biopsy report, the exact anatomical classification should be determined. The stage of the lesion at the time of the initial examination should be maintained throughout the entire period of treatment and observation, regardless of regression or progression; that is, a Stage IV lesion may, during proper treatment, shrink to the extent of Stage II, or almost completely disappear, but the records should continue to show it in its original classification, Stage IV. It is necessary for prognostic value that the result of the treatment be evaluated in terms of the lesion as originally seen.

STATISTICAL SURVEY

The following group of consecutive cases has been treated in the Department of Radiology, St. Luke's Hospital, during the period 1936 to 1945. The total number of cases seen is 58. Of these, 4 are excluded immediately because of failure to have

* From the Department of Radiology, St. Luke's Hospital, Chicago, Illinois.

more than one or two treatments. Of the remaining 54 cases the follow-up is not sufficient in 9 to permit inclusion in the final tabulation. Therefore, 45 cases comprise the effective number of cases that are available in this series for statistical evaluation.

The last column on the right of Chart IV shows the overall results of the entire group, and is further elucidated by Table I.

Table II shows the age of the cases by decades at the time of the biopsy. The average age of all cases is 57.6 years with the youngest case thirty-four years of age and

CHART I

ANATOMICAL CLASSIFICATION OF CANCER OF THE LARYNX FOR USE IN RADIATION THERAPY

RIGHT				*LEFT*
PYRIFORM SINUS ARYEPIGLOTTIC FOLD Extrinsic		EPIGLOTTIS		PYRIFORM SINUS ARYEPIGLOTTIC FOLD Extrinsic
Intrinsic				Intrinsic
A	FALSE CORD	A C	FALSE CORD	A
R		N O		R
Y		T M		Y
T		E M		T
E	VENTRICLE	R I	VENTRICLE	E
N		I S		N
O		O S		O
I	TRUE CORD	R U	TRUE CORD	I
D		R		D
Intrinsic		E		Intrinsic
Extrinsic				Extrinsic

THYROID
CRICOID

Stage I: Involvement of any one area only
Stage II: Involvement of any two *adjacent* areas
Stage III: Involvement of any two *non*-adjacent areas or any three adjacent areas
Stage IV: Involvement of more than three areas, the regional glands or distant metastases

"INTRINSIC" will be added to the classification when the neoplasm does not extend beyond the dotted lines; if it does extend either above or below the dotted lines at any point then it automatically becomes "EXTRINSIC."

The classification should be made at the time for the *first complete* examination and not changed during treatment, so that one may evaluate the effect of the therapy in terms of the extent of the original lesion.

Charts II and III graphically demonstrate the results in the 45 cases. They are first divided into intrinsic and extrinsic types and then further broken down into the anatomical stages as described above; Chart II showing the actual number of cases alive and dead at the time of writing, and Chart III showing the average monthly survival for each of the subdivisions.

Chart IV shows the results of the same 45 cases when they are broken down into only the anatomical stages and not into the intrinsic and extrinsic types as well.

the oldest eighty-six years. It is easily seen that the onset of this disease is most frequent in the fifth decade of life.

Ten patients, or 22.2 per cent, had a tracheotomy while under observation, 6 of them before the treatment and 4 after the series was started.

Three patients, or 6.7 per cent, required gastrostomy.

Laryngectomy was performed on 2 patients before the treatment and on 2 after treatment. The latter were operated on for local recurrences that probably were not

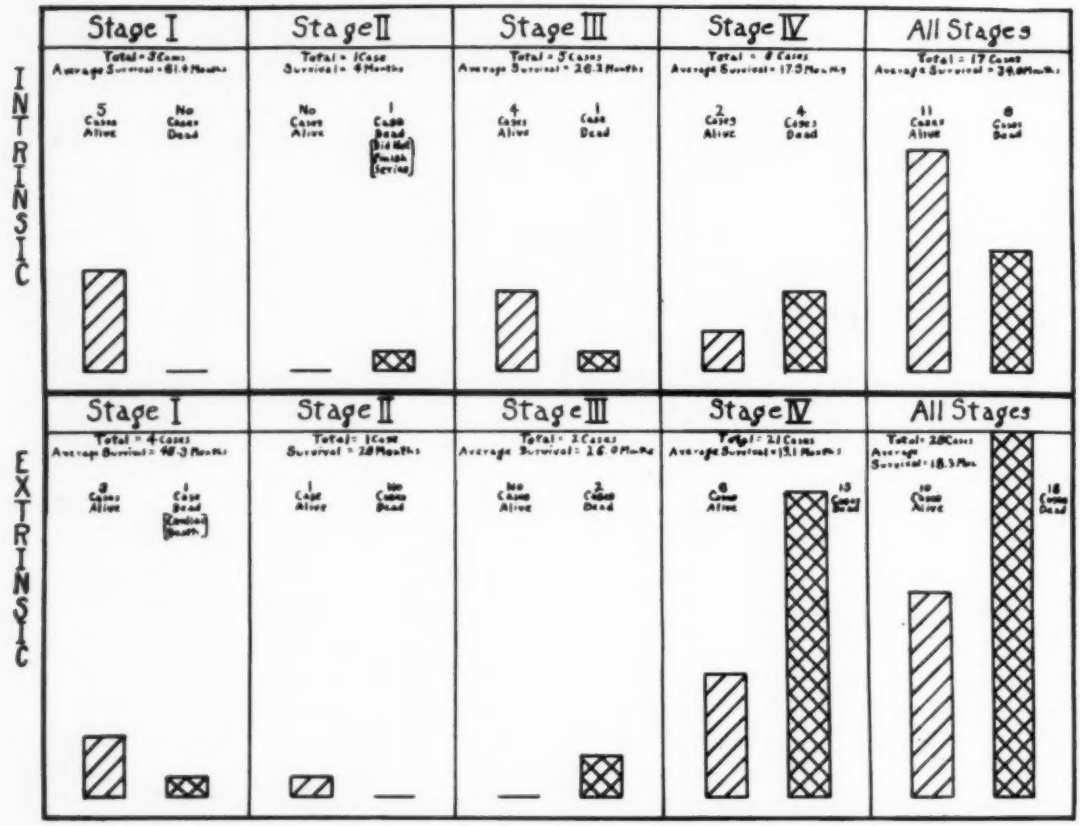

CHART II. Mortality of cancer of the larynx divided anatomically.

true recurrences but new tumors as one occurred some four and one-half years after the original treatment. The former 2 cases had laryngectomy and within short periods local metastatic lesions appeared in the cervical glands.

Two cases, or 4.4 per cent, had laryngeal fissure followed by recurrences in short periods for which the radiation was administered.

Table III shows the three, five, and ten year results of this small series. The percentages given refer, of course, to the number of survivals per treated cases that

TABLE I

PERCENTAGE SURVIVAL OF ALL CASES

	Cases Dead	Cases Living	All Cases
Number of cases	24	21	45
Average survival	12.2 mo.	36.5 mo.	24.1 mo.
Per cent of total	53.3	46.7	100

TABLE II

NUMBER OF CASES PER DECADE AT TIME OF BIOPSY

Years	30–39	40–49	50–59	60–69	70–79	80–89
Number of cases	2	9	14	10	9	1

TABLE III

THREE, FIVE AND TEN YEAR RESULTS

	3 Year Observation	5 Year Observation	10 Year Observation
Number of cases	25	15	2
Number of survivals	8	3	1
Per cent survivals	32.0	20.0	50.0

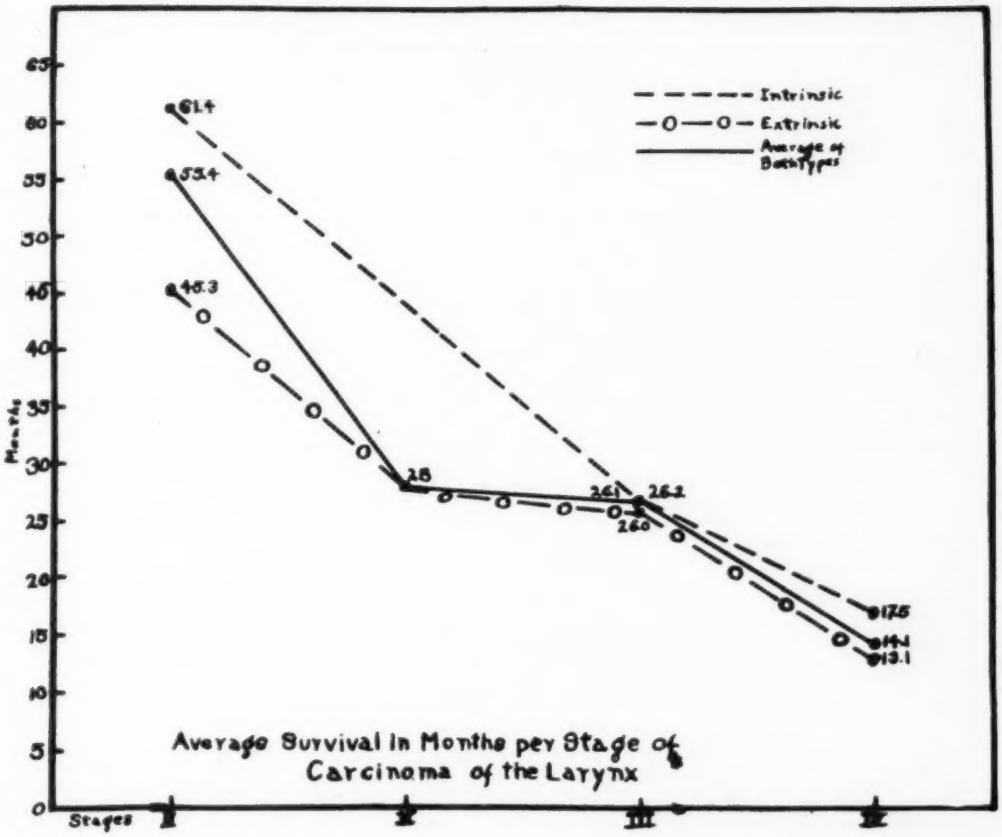

Chart III. Average survival in months per stage of cancer of the larynx.

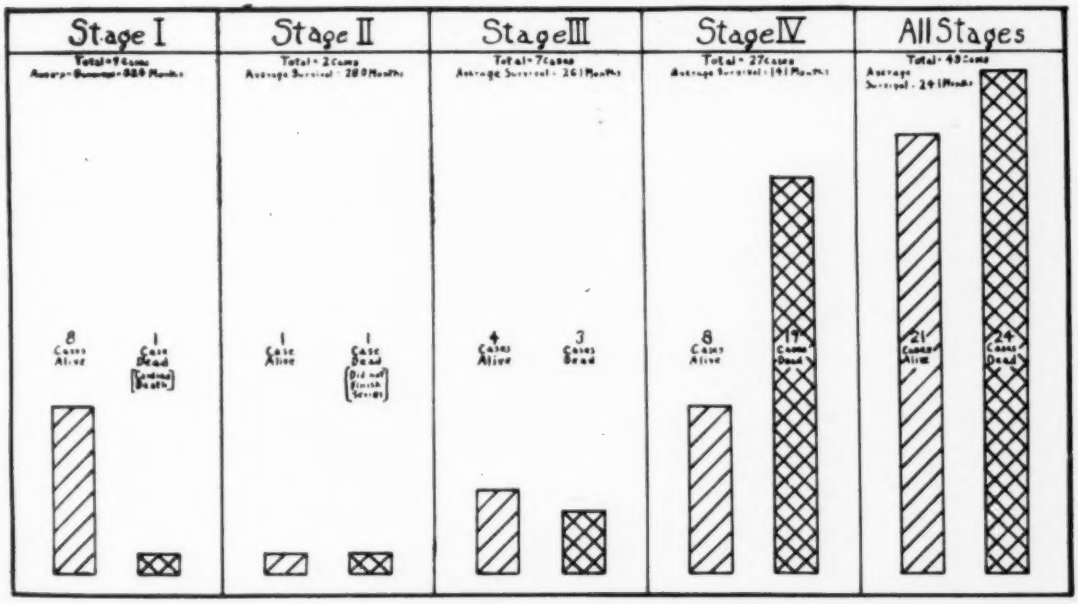

Chart IV. Mortality of cancer of the larynx divided surgically and anatomically.

could have lived that length of time. The ten year survival rate of 50 per cent shows the marked fallacy of dealing with small numbers of cases. The three and five year rates are thought to be reasonably representative of this condition.

TECHNICAL FACTORS

The technical factors used over the years with little variation consist of 200 kv. (peak), mechanically rectified, 20 ma., Thoraeus filter (0.40 mm. tin, 0.25 mm. copper, and 1.0 mm. of aluminum), 50 cm. target-skin distance, a round cone measuring 10 cm. in diameter directed at the mid-portion of the larynx through lateral portals, 20 r per minute delivered with a daily dose of 200 r (measured in air) to a single field. The total air dose to each field is 3,800 r at present. Quimby's depth dose tables give for an average 6 cm. larynx a tumor dose of 102 per cent of the air dose at 3 cm. This gives a total tumor dose of 7,752 r.

Definite evidence of radiation necrosis has not been seen in this series. A marked skin reaction occurs in the majority of the cases but clears quickly at the conclusion of the series of treatment. Edema of the laryngeal mucosa sometimes persists for several months to years, but no permanent untoward results have been observed from this condition.

DISCUSSION

Fifty-eight cases of cancer of the larynx are reported, of which 45 cases have received adequate follow-up to permit a statistical survey with the use of an anatomical classification by extent designed to be of value in the prognosis of cases when treated with radiation.

We wish to make clear that the intrinsic and extrinsic classification of these tumors offers little of value to the radiologist, but that it is the extent of the lesion when first seen and not the location that is the most important radiotherapeutic prognostic point.

Chart IV shows that of 11 early cases treated with radiation, 2 are dead at the present writing. One of these died of cardiac disease within two months of the completion of the series, and the other had less than half of the projected treatment when he failed to return for the remainder. So that we may say that in the early cases, that is those of small extent which received adequate treatment, we have had no deaths due to the cancer. The laryngologist's report at the time of the last examination of all the early cases shows no evidence of neoplasm in the larynx and the average monthly survival of these cases at the present writing is 55.4 months. Since none of them at present show demonstrable tumor, it is felt that they have a good many more fruitful years of life remaining.

CONCLUSION

1. A consecutive group of 58 cases of cancer of the larynx is presented with a complete follow-up on 45 of the cases, permitting a rather detailed statistical study.

2. The fallacy of radiologists using a surgical classification is pointed out, and a new classification is offered as being of great value in the prognosis of these cases.

3. The authors are quite impressed with the excellent results obtained in the early lesions and have found that the earlier in the disease radiation treatment is instituted, the better the result.

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ACCUMULATION OF BLOOD SIMULATING PRIMARY BRONCHIAL CANCER

REPORT OF CASE

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NUMEROUS factors contribute to production of the density visualized in the thorax on roentgenoscopic study of a malignant lesion in a bronchus. Small tumors in a bronchus frequently cause diffuse areas of infiltration because of atelectasis of the pulmonary tissues, retained secretions, and associated inflammatory reaction, whereas large tumors may reveal small areas of density because of absence of obstruction and infection. Small benign tumors or foreign bodies often produce shadows and cause physical signs that are indistinguishable from those created by the presence of malignant intrabronchial growths.

Diffuse infiltration at the base of one lung revealed by roentgenoscopy with associated diminution in breath sounds is usually thought to be caused by intrabronchial tumor because of the relative frequency of primary bronchial malignancy. The fact that blood may accumulate in the tracheobronchial tree as the result of suppression of the cough reflex and give rise to findings identical with an intrabronchial malignant growth is not generally appreciated and prompts the following case report.

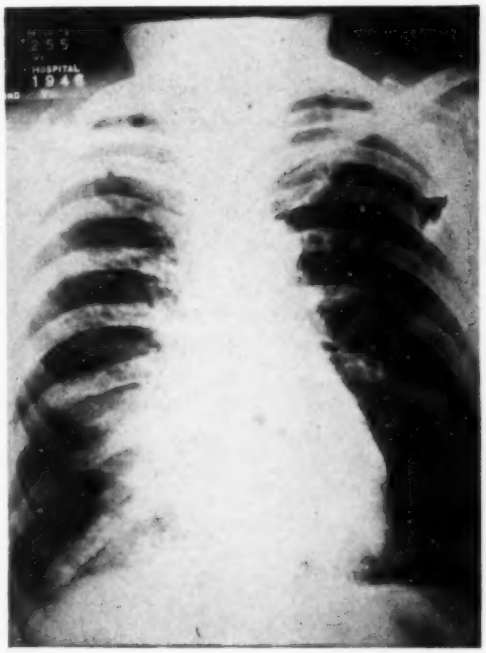

FIG. 1. Roentgenogram, May 5, 1946, showing diffuse infiltration at base of right lung, extending from the hilar area.

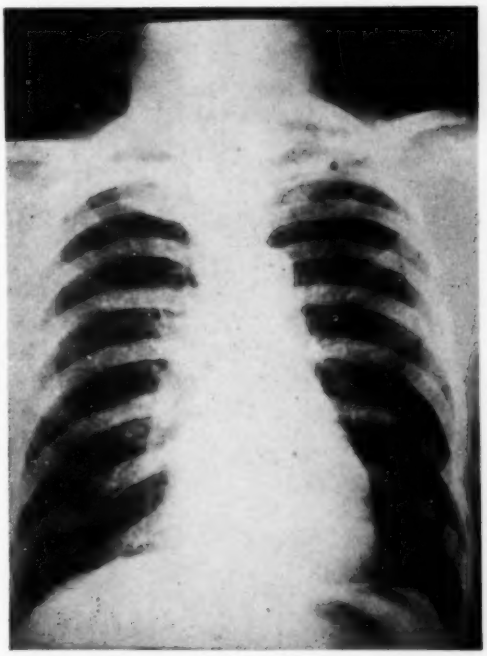

FIG. 2. Roentgenogram, June 5, 1946, showing no abnormality of thorax.

REPORT OF CASE

A white male, aged fifty-five, was admitted to Stuart Circle Hospital on May 4, 1946. Al-

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though he was not particularly robust, he considered his health good and had maintained a weight of 134 pounds for several years. In 1918 he had coughed up a small amount of blood that was thought to have come from his nose. For four years he had had occasional, nonproductive cough which had become more pronounced three weeks prior to hospitalization.

On May 1, 1946, on retiring, he began to cough dark, clotted blood and then bright red blood, about a cupful in all. The following day he coughed up another cupful of blood, and on May 4 he expectorated enough blood to fill a large emesis basin. Two doses of morphine were administered hypodermically. He continued to have a slight cough with expectoration of small amounts of bright red blood.

Physical examination revealed impairment of percussion note and diminished breath sounds over the lower lobe of the right lung posteriorly. Roentgenoscopic examination showed diffuse infiltration at the base of the right lung, extending from the hilar area, and the condition was interpreted as primary bronchial cancer (Fig. 1). The patient's temperature was 100.4° F. Laboratory studies disclosed essentially normal findings, and there was no reduction in the amount of hemoglobin nor in the number of erythrocytes.

Because of the continuation of pulmonary hemorrhage, bronchoscopic examination was performed on May 6, 1946, and after removal of blood clots, active bleeding was found to be coming from a posterolateral division of the bronchus to the lower lobe of the right lung. This bronchial division was thoroughly curetted and dilated, and several cubic centimeters of a 1 per cent solution of neosynephrin were instilled into the bronchial lumen.

Bleeding stopped at once, and for the past seven months the patient has been perfectly well. A second roentgenogram of the thorax on June 5, 1946, did not reveal any abnormality (Fig. 2).

The cause of the bleeding in this patient was simple bronchial erosion.

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RADIOTHERAPEUTIC ERADICATION OF CANCER WITH SURGICAL REPAIR OF SUBSEQUENT ULCERATION AND DEFORMITY*

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THE primary essential in the treatment of cancer is the complete eradication of the malignant neoplasm. The other important consideration is maintenance of subsequent disability, distress and deformity at a minimum. The radiotherapist must frequently chart a precarious course for his patient. On the one hand lies the abyss of oblivion in cancer, while on the other is the devil of post-irradiation sequelae. Threats of trouble from post-irradiation complications in certain cases tend to restrain the therapist from administering sufficient radiation to control cancer, and as a result the patient is victimized by his disease. The complications and sequelae of cancericidal irradiation must be accorded intelligent consideration and discerning judgment by patients, courts and doctors if radiotherapy is to make its full contribution to the control of cancer.

A program of aggressive radiotherapy followed by plastic repair is greatly facilitated by a frankly informed patient and consultation with a cooperative surgeon. Allowing the patient insight as to the true nature and potentialities of his disease usually insures his cooperation, respect and forbearance. The poorly informed patient may at times misinterpret the protective evasiveness of his doctor as evidence of professional incompetence or even malicious deception. In this resentful state of mind, he is more unhappy and morose than the patient who knows that he has a cancer and realizes that strenuous measures must be directed toward control of his disease. As a rule, the informed patient soon develops a complacent philosophy, undergoes treatment courageously, and accepts the associated incovenience and complications without complaint. It is highly desirable that the patient be informed as to the slow response of the lesion, the anticipated reactions to irradiation, and in certain cases, forewarned of uncertain healing and the possible need for subsequent plastic surgery. Enlightened forbearance and intelligent cooperation in the patient permit more adequate treatment of the cancer, better management of any ensuing complications, and avoidance of subsequent misunderstandings.

Consultation between the surgeon and radiotherapist is advantageously held prior to administering treatment whenever there is probability of combining irradiation and surgery. In case post-irradiation plastic repair is anticipated, it is well to have surgical consultation preceding radiotherapy. So, likewise, in case postoperative or supplementary radiotherapy seems indicated, the radiotherapist should be consulted before rather than after operation. Pretherapeutic consultation occasionally will modify the therapeutic plan, lead in some cases to treatment by either surgery or radiotherapy alone, and in others to an unanticipated combination of the two methods. Surgery and irradiation should be considered supplementary rather than competitive in the treatment of cancer.

The physiobiology and general management of chronic ulceration occurring after irradiation has been reviewed by us in a previous presentation.[21] It has been pointed

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out that chronic ulceration is contributed to by numerous constitutional, regional, cytological and environmental influences, many of which are not subject to control by the radiotherapist. Persistent or recurrent ulceration is to be anticipated after eradication of cancer in infirm patients, from regions devitalized by poor blood supply, infiltrated by infection, damaged by trauma or invaded by extensive cancer. Such chronic ulcers are not the direct result of excessive irradiation, but rather are due to inadequate recuperability of the tissues. The reference to such lesions as "x-ray burns" by many radiologists and by most surgeons is not only erroneous but also provocative of malpractice suits. Unfortunately, the term "x-ray burn" in the lay mind has implied negligence with gross overexposure and disaster. Chronic ulceration developing subsequent to irradiation is not in itself evidence of faulty radiotherapy.

FACTORS INFLUENCING TISSUE REPAIR

The influences which may contribute to any persistent or recurrent ulceration following irradiation are: (*a*) constitutional disease—particularly hypoproteinemia, anemia, vitamin C deficiency, arteriosclerosis, and uncontrolled diabetes and syphilis; (*b*) inadequate blood supply—peculiar to certain regions, reduced by surgical ligation or impaired by previous irradiation; (*c*) infection infiltrating devitalized tissue by way of surface ulceration; (*d*) foreign body effect of necrotic bone, cartilage or fascia; (*e*) trauma, whether actinic, thermal, mechanical or chemical; (*f*) inadequate regeneration of tissue due to inherent cellular derangement or exhaustion by excessively large diseased area; and (*g*) residual or recurrent neoplasm. Every precaution should be utilized before, during and following radiotherapy to conserve vascularity, normalize nutrition, minimize infection, avoid unnecessary trauma, and promote the regeneration of tissue. Radiotherapy must be administered in sufficient dosage for destruction of cancer, with an average requirement of about 7 to 10 erythema doses. The timing and space distribution are to be so regulated as to favor recovery of the normal tissues, as far as possible.[19,21,36]

The general management of ulceration occurring after irradiation involves observation of the above precautions. Nutritional deficiencies and anemia should be corrected and systemic diseases controlled as far as practical. Ligation of regional vessels should be avoided when possible. Vasodilating drugs have no appreciable effect in the promotion of blood supply through irradiated areas. Peri-arteriolar sympathectomy has been credited with improved circulation and healing of some post-irradiation ulcers.[21] Infection is minimized by delaying the onset and reducing the severity of acute radiodermatitis through more prompt healing of the skin. Secondary infection is best treated by bland wet dressings fortified by such bacteriostatic or antibiotic drugs as may be indicated.[21,22] Necrotizing soft tissues can sometimes be eliminated through oxidation with azochloramide or zinc peroxide, or by lysis with allantoin or urea. Sequestrating cartilage and bone may be expelled spontaneously or in some cases may require removal by cautery or excision.

The regeneration of epithelium across indolent ulcers is most effectively promoted by radon ointment, as advocated by Uhlmann.[11,23,34] Had radon ointment been freely available to us, its application might have been effective in healing the majority of the ulcers which we have closed by surgical procedures. A period of two to sixteen weeks is required for the healing of ulcerated areas by radon ointment therapy. The method is reputedly effective in all lesions except those which involve bone and those ulcers complicated by residual or recurrent neoplasm.[35] It has the advantage of centering all responsibility in the hands of the radiotherapist. The entire procedure can be done without hospitalization of the patient and necessitates only a weekly visit to the doctor. The total expense will

usually be considerably less than the cost of comparable surgical procedures and hospitalization. Surgical closure can always be resorted to in case the response to radon ointment appears too slow or ineffectual. The possibility of residual carcinoma must be suspected in those ulcers which do not show improvement after three to five weeks of radon ointment therapy.

INDICATIONS FOR SURGICAL REPAIR

It is desirable that ulceration occurring in an irradiated area heal without undue delay in order to relieve the patient from pain, exclude infection from the devitalized tissues, minimize disfigurement and loss of tissue through necrosis, and prevent the development of malignant degeneration. Surgical treatment warrants consideration when ulceration persists for more than eight to ten weeks under good general and local management. A preliminary trial with radon ointment seems warranted in certain cases. Surgical closure is definitely to be considered in all ulceration persisting past three to four months and in cases with extensive necrosis.

Surgical closure of ulceration occurring in irradiated areas has certain advantages.[13] Excision of the margins and base of the ulcer preparatory to closure provides material for microscopic examination permitting detection of residual neoplasm. The possibility of subsequent malignant change is definitely decreased. The skin will be more durable and have a more normal consistency following surgical closure than with delayed spontaneous healing. Disfigurement can usually be more effectively corrected by plastic repair. The blood supply of the area may be benefited, particularly in those cases closed by a sliding flap or a pedicle graft. Necrotic tissue can be eliminated more promptly. The total period of ulceration is reduced, complete closure frequently being accomplished within ten days by excision and approximation, sliding flaps or split grafts. Lesions requiring pedicle grafts may necessitate two to three months for chain procedures in the elevation, vascularization, jumping and final attachment of the graft to the recipient area.

It is desirable that the radiotherapist be familiar with the methods and principles of surgical treatment of chronic ulceration[1,5,10,13,14,17,18,25] in order that he can better evaluate the possible effectiveness of surgical repair in the individual patient, and so that he may cooperate intelligently with his surgical colleagues. This basic knowledge should broaden the radiotherapist's conception of cancer therapy and enhance his value as a consultant. A working knowledge of the possibilities of plastic repair permits the radiotherapist to be more aggressive in the treatment of selected cases of inoperable carcinoma, and it opens a positive hopeful approach in the management of post-irradiation ulceration and necrosis. Not infrequently, there is a tendency to blame previous irradiation for the failure of plastic surgical procedures when the real fault may lie in the surgical technique and clinical management. In such cases, the informed radiologist may offer constructive suggestions for the overcoming of difficulties, rather than mutely accept an explanation that the grafts failed to survive because of the previous irradiation.

PREPARATION OF ULCER FOR GRAFTING

Successful closure of an ulcerating area by plastic surgery requires (1) proper preparation of the ulcer bed, (2) selection of appropriate method or type of graft, (3) preparation of viable graft, and (4) establishment of it in the recipient area. Hypoproteinemia, anemia and other systemic disorders which may seriously retard wound repair should be corrected. Undue delay of soft tissue closure increases tissue loss through progressive infection, reduces blood supply and enlarges the area which must be subsequently grafted. It is essential that cancer shall have been completely eradicated from the ulcer bed; otherwise the graft will fail or cancer will recur subcutaneously beneath the graft. Persistent

cancer is suggested by hemorrhagic, friable induration.

The recipient area must be cleansed of infection and the necrotizing tissue eliminated. Wet dressings fortified by penicillin (200 units per cc.) or tyrothricin (0.5 mg. per cc.) is helpful in the suppression of gram positive bacterial growth. Application of strong antiseptics to the area further damages the already devitalized tissue, thereby increasing necrosis with little, if any, restraint of bacterial growth. Necrotic soft tissues can be partially eliminated through use of azochloramide, activated zinc peroxide, allantoin or urea.[21] An ointment consisting of 2 per cent allantoin and 10 per cent sulfathiazole in a water soluble base, or a sterile powder composed of one part micraform sulfathiazole in three parts of urea may be helpful in reduction of infection and elimination of some loose necrotic tissue. Electrocautery is useful for the elimination of necrotic soft tissues and is usually followed by alleviation of pain. Debridement, in addition to reducing infection and eliminating necrotizing tissue, exposes healthier vascular trunks, thereby promoting better vascularization and regeneration of granulation tissue. The organizing fibrinous membrane and excess granulation tissue seen in the more recently treated areas must be curetted away or shaved off for exposure of a healthier base to which the skin grafts can be applied. The devascularized and atrophic marginal skin must be excised back to healthy tissue preparatory to attempting surgical closure. Necrotic tissues must be excised from the base until a vascularized bed of viable tissue is exposed. The excised tissue should be examined histologically for evidence of residual neoplasm.

EXCISION AND APPROXIMATION

The various surgical procedures available for repair of cutaneous defects are excision and approximation, sliding flap, pedicle graft, and free skin graft. The simplest procedure is excision and approximation. The use of this method is limited to relatively small lesions and to those lesions which are bordered by abundant loose tissue, as in the mammary area. Success is dependent upon elimination of the diseased tissue and closure without excessive tension. Tension on the flap margins can frequently be relieved by adhesive or an arched bar applying traction 2 cm. or more distal to the line of closure.

Small superficial areas of ulceration frequently heal after electrofulguration and curettement with removal of the necrotic surface layer.

PEDICLE GRAFTS

Pedicle grafts are used for closure of defects from which there has been a loss of subcutaneous as well as cutaneous tissue and in lesions deficient in blood supply. Pedicle grafts were developed primarily by Gillies, who has used the method extensively in reconstructive surgery. Gillies and McIndoe[18] have successfully applied this method to the treatment of radionecrosis, and report that such lesions can be grafted as well as any other indolent ulcer. A pedicle flap is a strip of skin with subcutaneous tissue receiving its blood supply through attachment at one or both ends. The viability of the flap is dependent upon its longitudinal vascularity, which can be increased by preliminary elevation about ten days before transfer. In case the length of the flap is more than two or three times its width, one, two or even more preliminary elevations should be made prior to transfer in order to insure viability and prevent gangrenous necrosis. The improved viability of the delayed flap seems to result, not only from the improved longitudinal vascularity, but also from conditioning of the tissues to lowered oxygen tension.

Pedicle flaps are of various types, such as flat, tubed, gauntlet and lined. A flat pedicle presents a raw subcutaneous surface, while in the tube graft the subcutaneous surface is covered by approximation of the rolled outer margins of the flap. The underlying skin surfaces from which the flap was elevated are sutured together or

covered by a free graft as in Case IX. The lined flap is covered on both surfaces by epithelium and is useful in the closure of perforating defects, such as a hole in the cheek. The undersurface of the flap may be covered by attachment of a split graft, by turning the end of the flap back upon itself, or by means of another pedicle flap. A gauntlet flap is particularly useful for application of grafts to the hand. The hand is simply slipped beneath the strap of skin which remains attached at each end (Case I).

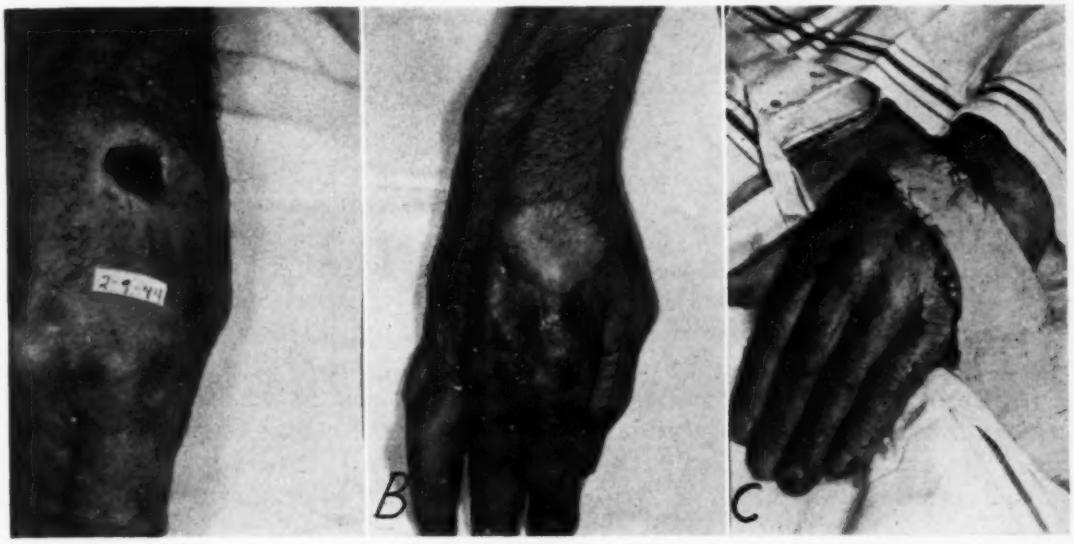

FIG. 1. Case I. W. J., farmer, aged seventy-four. Deep ulcer dorsum of hand repaired by pedicle flap. Squamous cell carcinoma, 3 cm., removed by 4×1,400 r in tissue, 80 kv. (constant), 2 mm. Al, in December, 1943, healed in eight weeks. *A*, February, 1944. Necrotic ulceration exposing metacarpal bone developing in healed skin after trauma fourteen months later. Excised ulcer showed no carcinoma. *B*, July, 1944. Plastic repair by a pedicle flap from abdomen. *C*, gauntlet type of pedicle flap, adaptable for closure of deep ulcer on dorsum of hand.

The sliding flap is a modified type of approximation in which a flap from an adjacent area of looser tissue is swung into the site of excision while remaining attached by a broad pedicle. The secondarily exposed area may then be closed by a split graft or a secondary plasty. This method has the advantage of often permitting immediate closure of a wide defect under less tension than would be possible with direct approximation. Furthermore, it closes a devascularized defect with more certainty and greater durability than a free graft. It is particularly valuable for closure of excisional defects in areas of limited tissue with nearby loose tissue, as in the case of the perineum and neck (Case VIII).

The sliding flap can be transferred from an adjacent area in one stage. The transfer of grafts from more remote regions will require two or more procedures. A flap may be jumped to an extremity and thereby carried to the recipient area. The free end of the flap is sutured to the defect and about two to three weeks allowed for vascularization before the base is divided and transferred entirely to the recipient bed. Immobilization between stages is imperative and may require plaster fixation.

The essentials of success in the preparation, transfer and implantation of pedicle grafts are adequate vascularization of the pedicle, avoidance of excessive tension, control of infection, and proper preparation of the recipient area. Vascularization may be inadequate due to the pedicle being too long in proportion to its width or from lack

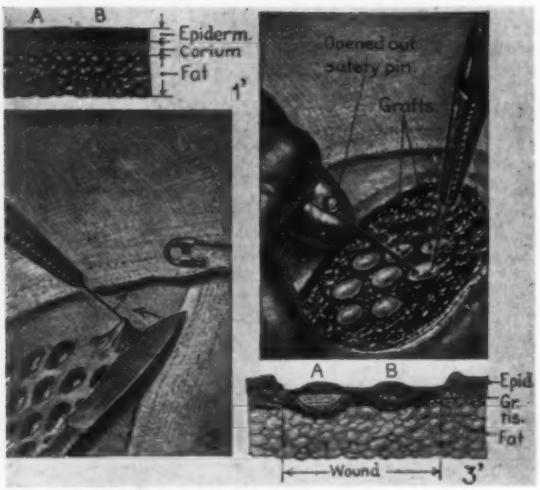

FIG. 2. Technique of sectioning and applying multiple small deep grafts (after Davis).

of preliminary elevation of the flap before transferring it. Constriction of the base of the pedicle by undue torsion or pull from excessive tension will also cause ischemia and may lead to gangrenous necrosis of the flap. The graft should be of proper size and shape to cover the defect without tension. All those factors enumerated under the physiobiology of ulceration influence the healing of wounds and determine the success of plastic surgery.

FREE SKIN GRAFTS

Free skin grafts are thin epithelial layers which have been separated completely from their original blood supply and placed directly on a freshly exposed subcutaneous surface where they must re-establish vascular communication with the underlying tissue. Free grafts are of three general types: multiple small deep grafts, split thickness grafts and full thickness grafts. The multiple small deep grafts,[15] commonly called "pinch grafts," consist of small discs of skin sectioned by cutting tangentially through a papule elevated with the point of a needle. Peripherally these grafts extend only through the epidermis, while centrally they extend down through the epidermis, dermis and into the subcutaneous tissue, as shown in Figure 2.

FIG. 3. Case 11. G. H., engineer, aged thirty-two. Precautionary application of multiple small deep grafts for prevention of chronic ulceration following intensive radiotherapy to postoperative residual fibrosarcoma of buttock. *A*, June, 1944. Subacute radiodermatitis six weeks following delivery of 14,676 mg-hr. radium (9,000 gamma r) plus 2,000 r in tissue, 200 kv. (peak), half-value layer 1.0 mm. Cu, during three weeks to a 3 by 5 by 9 cm. infiltrating tumor. *B*, Two weeks later. Area fully epithelized by multiple small deep grafts with relief of pain. (Thick split graft would now be preferred.) Patient well three years later.

The main advantage of the small deep graft is the simplicity of the method and its adaptability in poorly vascularized, somewhat infected areas. The disadvantage is the poor cosmetic result, both in the donor site and on the grafted area, as shown in Figure 3*B*. The full thickness graft has the serious disadvantage of poor viability and loss of capacity for regeneration of epithelium in the donor site. In the case of split grafts, regeneration occurs from the germinal layers of the hair follicles (Fig. 4).

Split grafts of uniform thickness provide the advantages of expediting closure, a good cosmetic result and fairly good assurance of success. The thickness of the split graft may be varied from the level of the epidermis to the deeper layers of the corium. The thin Ollier-Thiersch graft will survive in the least vascular bed, but has the disadvantages of lacking durability and of contracting after application. The deep uniform thickness split graft cut just above the lowermost limits of the corium provides a more durable surface and still permits primary regeneration of epidermis at the donor site. The technique of intermediate split grafts has been developed primarily by Blair and his coworkers.[3,4,5,6] A split sheet graft can be sectioned freehand according to Blair's technique or sectioned mechanically with the Padgett dermatome.[28] The graft must be cut to a size slightly larger than the defect to be closed as some shrinkage always occurs. The Padgett dermatome consists of a metal drum to which the donor skin is glued preparatory to section by the attached razor which is moved to and fro in a fixed slide set at calibrated depths. The thickness of the skin varies with age, being as little as 0.01 inch thick in a child, 0.02 inch in the aged, and as much as 0.04 inch in adults of young and middle age. We have employed grafts of an average thickness of 0.02 inch, classified as deep intermediate split grafts.

Fig. 4. Diagram of the skin showing different levels of section for various free grafts. Epidermis is regenerated from hair follicles and glands.

Fig. 5. Padgett dermatome glued to donor site preparatory to removal of a split sheet graft of calibrated thickness.

Split grafts can be applied to the recipient bed by prolonged application of pressure[3] or by thrombin-plasma fixation.[32,37] The pressure method requires complete hemastasis, exclusion of blood and serum from between the graft and the recipient bed, and the prior elimination of infection from the ulcer bed. Blair advocates a pressure equivalent to 30 mm. of mercury.

Pressure can be applied with sponge rubber or mechanic's waste held in place by adhesive. Occasionally the sutures maintaining the graft in contact with the margins of the bed are tied upward across the dressing to maintain pressure. The success of split grafts has been promoted through the adherence of grafts to the bed by thrombin-plasma fixation. Thrombin is applied to the recipient area, either as a dry powder or in solution (7.5 mg. per cc.). No sulfa powder, penicillin, saline or other material is permitted in the recipient area. Thrombin must be applied immediately before the graft is set in place, since thrombin coagulates blood in two to three seconds. The split graft is immersed in plasma and carefully applied to the recipient area as soon as the thrombin has been applied. The graft must be perfectly placed, since it cannot be moved after being once set in position without breaking its fixation. The thrombin-plasma method eliminates the dead space between the graft and recipient bed, thereby preventing the accumulation of blood and serum there. It is not necessary to suture the graft to the margins of the donor site in this method, little pressure is needed and in most cases a simple sterile dressing suffices. The area should be protected and immobilized so that the graft is not loosened by trauma or movement.

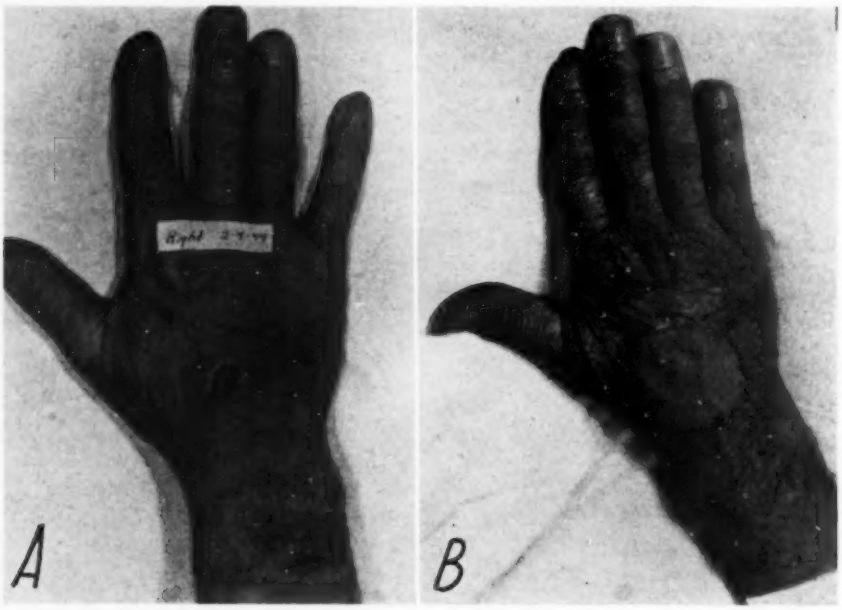

FIG. 6. Case III. A. M., lumberyard man, aged sixty. Ulcer on dorsum of hand repaired by deep split graft. Squamous cell carcinoma, Grade 1, 2.5 cm. across, removed by 3,600 r in tissue, 80 kv. (peak), 0.5 mm. Al, in November, 1941, with prompt healing. *A*, February, 1944. Ulcer occurring following trauma after being healed twenty months. Biopsy showed no carcinoma. *B*, July, 1944. Ulcer excised and thick free graft implanted in the base.

Successful implantation of a free split graft requires proper preparation of the recipient area, sectioning of the graft through the correct level, and firm adherence of the graft to the recipient bed. Devitalized tissue must have been eliminated from the bed of the ulcer and its margins excised back to healthy tissue. In case the recipient area is fairly vascular, the split graft may be sectioned to the deeper layers of the corium, but definitely not to the subcutaneous tissue. The poorer the vascularity of the recipient area, the thinner the graft needed for viability. The most important detail in insuring successful adherence of a split graft in the pressure method of

TABLE I

REGIONAL AND DEVITALIZING FACTORS CONTRIBUTING TO ULCERATION AND NECROSIS

Region Involved by Carcinoma	Hand (5) Forehead (3)	Ear (3) Nose (2) Larynx (2) Rib (1)	Lip (4) Gum (2)	Vulva (1) Anus (1) Penis (1)	Sarcoma (5)	Neck (3)	Total
Total	8	8	6	3	5	3	33
Persistent ulcer	2	2	1	1	4	1	11
Recurrent ulcer	6	6	5	2	1	2	22
Contributing factors:							
1. Devascularization							
(a) Over bone or cartilage	8	8	2				18
(b) Previous Surgery	4	2	2		5		13
(c) Previous irradiation	2	3	3	1	4		13
2. Infection							
(a) Osteochondritis	2	8	2				12
(b) Contamination			4	3			7
(c) Delayed closure	4			1	1	3	9
3. Trauma							
(a) Mechanical, etc.	6		2			2	10
(b) Sunburn	4	4	4				12
(c) Freezing		4					4
4. Area over 4 cm.	3				5	3	11

implantation has been correct application of even pressure for a period of five to ten days. Insufficient pressure would permit serum to accumulate beneath the graft, separating it from its nutritive bed, with resulting necrosis of the graft from anoxia. Excessive pressure leads to necrosis from ischemia which is the common cause of failure in the thrombin-plasma method.

CASE ANALYSIS OF FACTORS CONTRIBUTING TO ULCERATIONS

The incidence of ulceration following radiotherapeutic eradication of malignant neoplasms will vary from 1 per cent upward depending on the type of case being treated, the aggressiveness of the therapist, and the timing and space distribution[31] of irradiation. In our experience, complications occur more commonly in dispensary patients than in private practice, which is attributed to: (1) the more advanced age and poorer general health of clinic patients, (2) greater frequency of previous inadequate surgery and irradiation, (3) more extensive and advanced disease, (4) necessary delegation of many technical details to individuals in training, (5) tendency to concentrate therapy and to reduce the number of treatments, (6) poorer hygiene and more exposure of treated areas to infection and trauma. Even with the best of radiothera-

peutic management, the period of healing will be prolonged and the incidence of recurrent ulceration will rise as efforts are made to control cancer in more advanced stages and eliminate disease from regions of marginal recuperability.

Analysis of 33 cases of ulceration occurring after radiotherapy shows prolonged lack of healing in 11 cases and recurrent ulceration occurring one month to six years after complete healing in 22 cases (Table 1). Recurrent ulceration occurred most frequently in those areas exposed to trauma by abrasions, as the hand and lip, or by blistering sunlight and freezing weather, as the lip, nose and ears. Trauma precipitates ulceration through introduction of infection into tissues of impaired vascularity. Tissues sustained by a barely subsistent vascularity or lacking in inherent recuperability are especially susceptible to virulent surface infections as in the hypopharynx or to persistent contamination as on the perineum. Vascularity may be reduced by previous incomplete surgery (as in 13 cases) or previous inadequate irradiation (13 cases).

The regions most commonly involved by recurrent ulceration are those composed of a layer of skin directly over bone or cartilage with little subcutaneous tissue. The arterioles in such areas as the dorsum of the hand, temple, scalp, nose, ear and gums, are of small size, and therefore particularly susceptible to stenosis by irradiation. Furthermore, there is a lack of nourishing subcutaneous tissues with no collateral deep circulation. All 11 cases showing persistent ulceration following eradication of neoplasms had lesions over 2.0 cm. across. In 8 cases the lesion was over 4 cm. in diameter. These large lesions deplete the regenerative capacity of epithelial and vascular tissues and widely expose the subcutaneous tissues to prolonged surface infection. In 3 cases lack of initial healing was due to associated infection of bone and cartilage (ear, costochondral junction, jaw). Altogether, infection of cartilage or bone was associated with post-irradiation ulceration in 12 of the 33 cases. In 3 cases chronic infection was aggravated by maceration and contamination (penis, vulva and anus). In other words, all irradiated lesions less than 4 cm. in size healed initially except those complicated by active infection in bone or cartilage. Perineal lesions healed very slowly and insecurely. Persistent or recurrent ulceration also may result from residual or recurrent neoplasm which can be differentiated by microscopic examination, and then only eight to ten weeks after therapy. Evaluation of the adequacy of radiotherapy will aid in differentiation between possible cancer and trophic ulcer, but is not fully conclusive.

CANCER OF THE HAND

Recurrent ulceration has been encountered on the dorsum of the hand in 5 cases after radiotherapeutic eradication of carcinoma. The disease usually has occurred in farmers and outdoor laborers well past middle age.[30] The skin is atrophic and devascularized from age and scarred from repeated trauma. The small caliber of arterioles and lack of subcutaneous tissue makes the region more vulnerable to irradiation and susceptible to trauma. Previous treatment had consisted of incomplete surgical resection in 4 cases and inadequate irradiation in 1 case. Carcinoma of the hand under 2 cm. and freely movable can be effectively eliminated by excision or irradiation. Excision is expeditious and provides a durable surface, although grafting is often necessary for closure. Lesions previously irradiated ineffectively are better excised and grafted since further irradiation commonly eventuates in subsequent breakdown after minor trauma. Lesions over 3 cm. and fixed to deep fascia are eliminated with more assurance by radiotherapy than by dissection.[7,30] Subsequent surgical repair may be needed to hasten epithelization and exclude infection. Braddon[7] reports remarkably uniform elimination of cancer from the hand with good healing of the skin in a series of 200 cases treated by low intensity radium moulds

continuously for two consecutive periods of seven days each. The secret of this success probably lies in the low intensity and in the good space distribution of radiation. In our cases which broke down following irradiation to cancer of the hand roentgen treatment was condensed to about four days or less and fractionation reduced accordingly.

ing bone, thereby predisposing the soft tissues to avascular necrosis following irradiation with exposure of the bone to infection. The basal cell lesions in this area progress slowly at first, seem innocuous, and may be neglected by the patient until quite extensive.

If the carcinoma is under 2 cm. and

Fig. 7. Case IV. G. M., farmer, aged eighty-two. Large infiltrating cancer of wrist, destroyed by roentgen irradiation with delay of healing. *A*, August, 1943. Fungating, excavated mass, 3 by 6 cm., received 6 × 1,200 r in tissue, 70 kv. (peak), 1 mm. Al. *B*, October, 1945. Slow gradual healing required fifteen months. Plastic repair refused.

In retrospect we feel that a lower daily dose and more fractionation would have promoted recovery without danger of persistent cancer.

Choice of method for repair of the dorsum of the hand depends on extent and depth of lesion. Few lesions are small enough for closure by approximation. Split grafts are expeditious and satisfactory for nearly all lesions on the hand (Case III). Pedicle flaps are considered only for lesions needing subcutaneous tissue, as on the palm or deeply excavated lesions (Case I).

CARCINOMA OF SCALP

Carcinoma of the forehead, temple and scalp also presents the problem of cancer occurring in a shallow vascular bed overly-

movable over bone, healing usually follows radiotherapy. If the lesion is over 3 cm., or fixed to bone, delayed healing and possible osteomyelitis with exposure of the skull may eventuate. Surgical closure over such areas of osteitis is usually unsuccessful. Primary surgical excision with closure by a sliding flap or split graft will usually close these larger scalp lesions unless there is invasion of periosteum or bone.

In case the lesion is fixed by infiltration of the periosteum or skull two methods of treatment are possible. The lesion can be treated by surgical resection down to the bone followed, first, by electrocoagulation of the outer table, then, by removal of the dead bone. This will expose the vascular diploic spaces which furnish a good bed for

a split graft. In case the lesion is treated by fractionated short distance radiation and healing is not occurring within six to eight weeks, the above surgical procedure may permit closure before osteomyelitis becomes established. Depth delivery should be kept low to minimize irradiation of the brain.

CARCINOMA OF NOSE

Carcinoma involving the bridge of the nose presents the problems of a shallow vascular bed and possible involvement of underlying bone. The nose develops an epidermolysis of both skin and mucosa, thereby opening entry for infection on both surfaces. We have seen infection enter from the mucosal surface into bone and perforate through to the skin. We endeavor to avoid irradiation of the septum and deeper tissues of the nose as far as possible by directing radiation tangentially and by introduction of lead foil covered by a lubricated finger cot upward along the septum. Recurrence of cancer of the nose following surgical and radiation therapy commonly results from unsuspected burrowing of cancer cells beneath the skin[27] and beyond the limits of therapy. Re-irradiation of the already devascularized tissue may be followed by slow healing or ulceration. Excision of recurrent and atrophic scar down to periosteum with immediate application of a thick split graft, as from behind the ear, will effectively control many lesions on the bridge of the nose. The repair of perforating lesions of the nose, and rhinoplasty in general, requires unusual skill and experience in the use of lined flaps, bone grafts and other special plastic techniques. Prostheses replacing the nose in whole or in part can be fashioned from latex, duroc and other plastics by experts or in cooperation with an interested and well equipped dental laboratory,[8,9,33] as shown in Figure 8.

FIG. 8. Case v. R. B., housewife, aged sixty-three. Restoration of facial contour with prosthesis. *A*, nose destroyed by syphilis and previous escharotic therapy for "cancer." *B*, nasal prosthesis prepared by Dr. A. M. Brown, Chicago, Illinois.

CARCINOMA OF THE EAR

The auricles of the ear and ala nasi likewise present only a thin layer of skin directly overlying cartilage. These areas

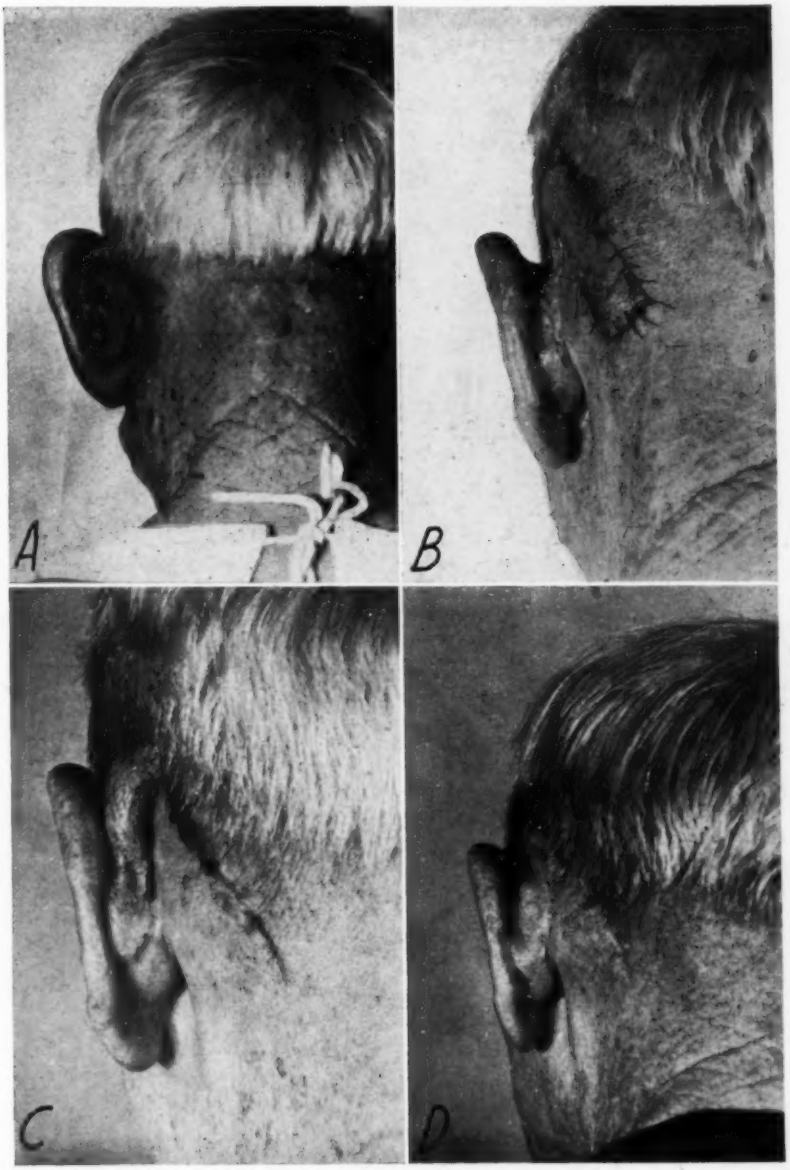

Fig. 9. Case vi. Js. B., laborer, aged sixty-nine. Necrosis of auricular cartilage following eradication of large carcinoma; chondritis excised, and defect closed by two-stage pedicle graft. *A*, November, 1943. Ulcerating mass on dorsum of ear, 2 by 4 cm., treated by 6×1,050 r in tissue, 80 kv. (peak), 0.5 mm. Al. Enlarged cervical nodes treated by radium interstitially—3,440 mg-hr. (8,600 gamma r). History of previous inadequate radiotherapy. *B*, July, 1944. Fair healing followed by ulceration exposing infected cartilage. Preliminary elevation of pedicle. *C*, two weeks later, Devitalized cartilage and skin excised. First stage transfer of pedicle flap. *D*, November, 1944. Completed transfer of graft and preservation of ear with excellent cosmetic result. Remains well in June, 1947.

not infrequently break down following concentrated irradiation due to endarteritic stenosis of the small vessels, predisposing to infection commonly introduced by freezing or sunburn, and resulting in a painful chondritis. In some cases of painful chondritis, we have removed infected necrosing cartilage for relief of pain and to permit healing of skin using scalpel or electrosurgical loop. Occasionally, it may be

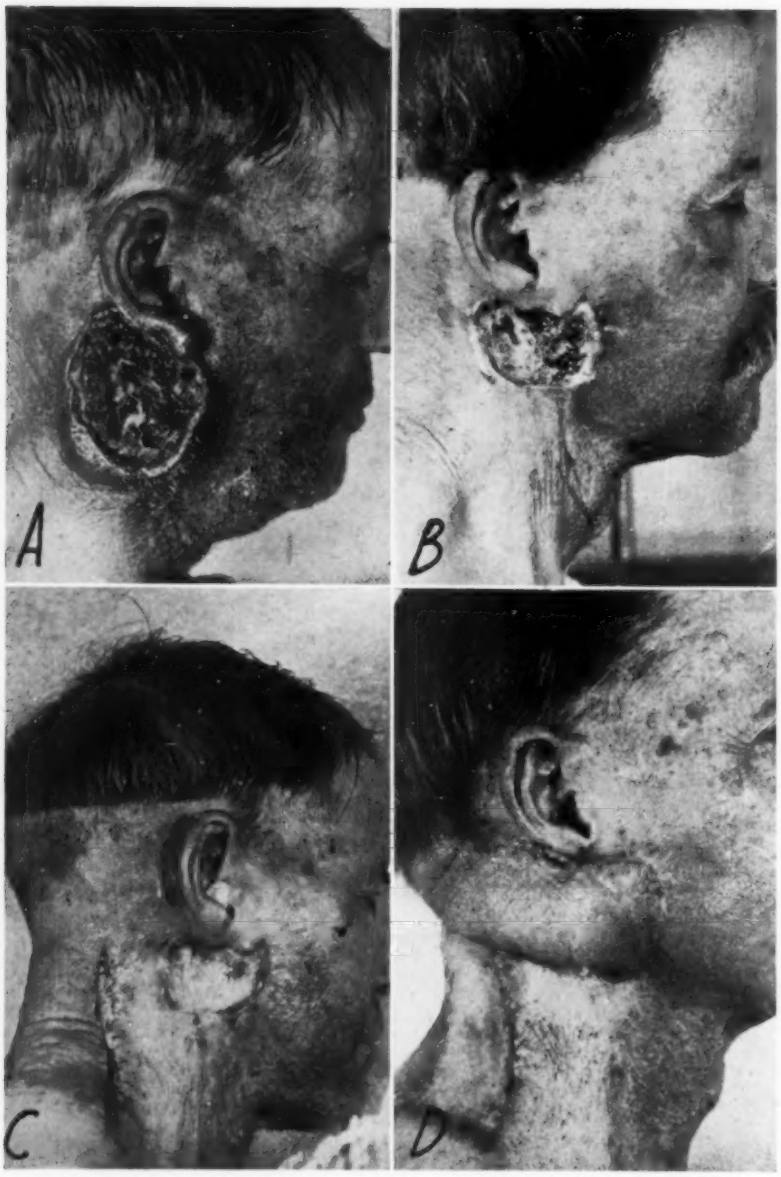

FIG. 10. Case VII. B. O., laborer, aged sixty-four. Large carcinoma of neck eradicated by roentgen and radium therapy. Repair of recurring ulceration by sliding flap with closure of donor site by split graft. A, ulcerating necrotic mass, 3 by 6 by 8 cm., received 12×450 r (5,400 r) in tissue, 180 kv. (constant), half-value layer 1.0 mm. Cu, plus 6,567 mg-hr. interstitial radium (5,000 gamma r) from July 13 to August 14, 1944. *B*, nine months later. Recurrent extension of ulcer after initial incomplete healing. *C*, pedicle flap elevated, and donor site covered by free split graft. *D*, ulcer excised, area closed by sliding flap. Well three years later.

possible to preserve the contour of the ear, as in Figure 9, Case VII. Some radiotherapists have claimed that cartilage was spared by high voltage, heavily filtered roentgen rays[26] and gamma rays.[24] It seems more probable that the better texture of tissues and lower incidence of break down is from lower intensity and greater fractionation rather than from shorter wave length. Cancer of the ear[16,24] and cancer of the nose[29] have been successfully treated by radiotherapy, but do carry some danger of subsequent chondritis, especially when fixed to underlying structures.

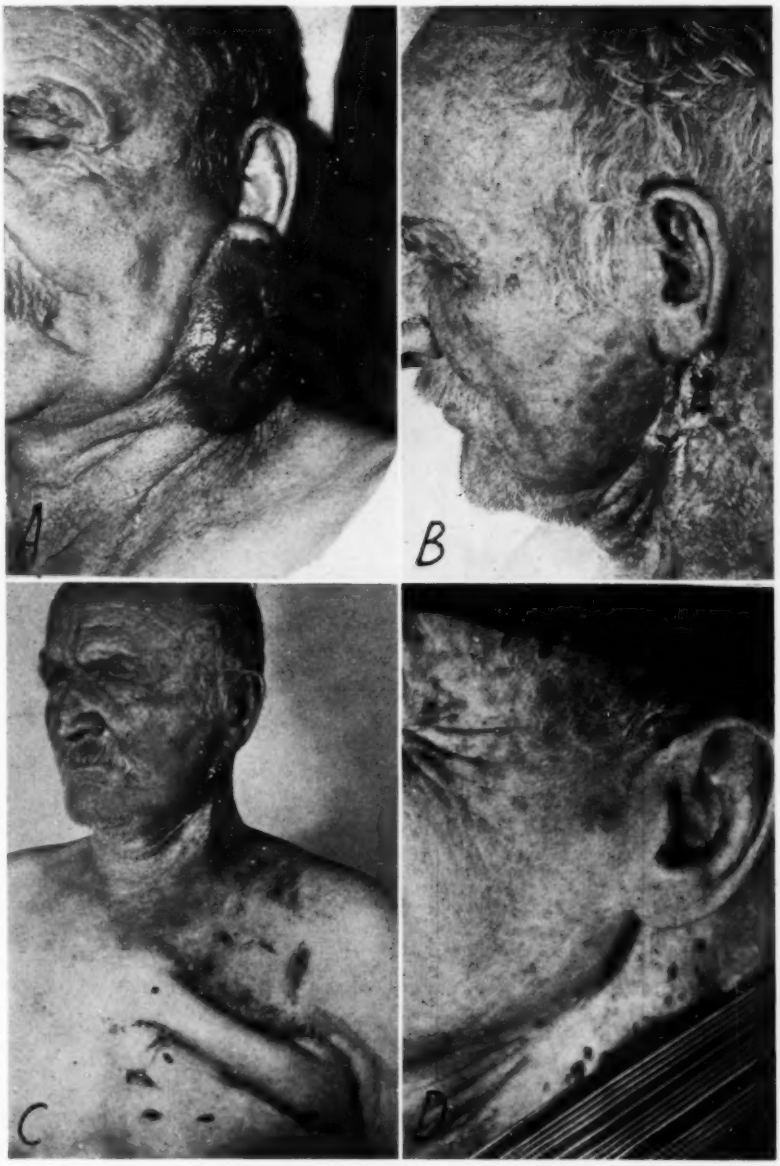

Fig. 11. Case VIII. Jn. B., confectioner, aged sixty-nine. Very large squamous cell carcinoma of neck eradicated by deep roentgen and radium therapy with very slow spontaneous healing. Patient refused transfer of pedicle flap raised in anticipation of surgical closure. *A*, April, 1944. Necrotic fixed mass, 5 by 7 by 10 cm., treated tangentially by 18×250 r (total 4,500 r) in tissue, 180 kv. (constant), half-value layer 2 mm. Cu, plus 3,218 mg-hr. interstitial radium, 0.5 mm. Pt (4,100 gamma r), all given from April 17 to May 17, 1944. History of previous inadequate radiotherapy. *B*, July, 1944. Carcinoma eradicated, ulceration persists with delayed healing. *C*, anticipatory tubed flap elevated from pectoral region was not utilized. *D*, July, 1946. Patient well, no evidence of carcinoma. Irradiated area healed slowly after one year. Patient refused surgical closure.

CARCINOMA OF LARYNX

Ulcerating carcinoma contiguous with the cartilage of the larynx presents even more difficult problems. We have encountered two fatal hemorrhages from recurrent ulceration of the larynx six months after irradiation by the "concentrated technique." Again, we believe that lower inten-

sity and more fractionation favor recovery of normal tissues and reduce the incidence of ulceration and chondritis. Radiotherapeutic eradication of carcinoma of the larynx actually infiltrating cartilage will usually be followed by a continuing chondritis and sore throat which may eventually heal, once diseased cartilage has been expelled. A laryngectomy done one year after irradiation resulted in complete break down of all suture lines. Special attention must be given to level of blood protein and adequacy of nutrition essential to wound repair in the case of cancer of the mouth and throat. Re-irradiation of carcinoma of larynx or hypopharynx carries greatly increased danger of subsequent chondritis, necrosis, edema and hemorrhage.

CARCINOMA OF THE MOUTH AND JAW

Carcinoma of the mouth adjacent to the jaw can usually be treated without too much hazard of osteomyelitis, providing teeth are extracted first. Extraction of teeth one month to ten years after intensive irradiation has led to sequestrating osteomyelitis of the jaw lasting for years and being aggravated by carotid ligation for control of hemorrhage. Since osteomyelitis and sequestration are to be expected in case there is actual invasion of the alveolus by cancer, in such cases electrocoagulation of the diseased bone will hasten its separation and allow more rapid closure of the wound. Osteitis of the alveolus usually is a self-limiting disease. Fractionated intraoral roentgen therapy and preliminary extraction of all sound, as well as diseased teeth in the exposed area has reduced the incidence of sequestrating osteomyelitis of jaw. Of course, the alveoli must be shielded when the lip and cheek are irradiated or a similar alveolitis may develop by way of dental sockets from pyorrhea or following extraction.

Perforation of the floor of the mouth or cheek following osteomyelitis or disintegration of a penetrating tumor usually can be closed by an expert plastic surgeon with a lined flap or plugged by a special prosthesis.

CARCINOMA OF THE LIP

The lip tolerates irradiation well and chronic ulceration is seen only after intensive re-irradiation following repeated blistering sunburn or trauma from misaligned or jagged teeth. Delayed breakdown occasionally follows irradiation of superficial linear ulcerations occurring in an atrophic mucous membrane seemingly sensitized to and repeatedly blistered by sunburn. In our experience this type of linear lesion may be excised by undercutting the mucosa with direct re-approximation of mucosa to vermillion border of the lip. Such lesions occurring in atrophic mucosa usually heal following roentgen irradiation or electrocautery, but ulceration may recur after blistering sunburn and adjoining areas often break down subsequently. Carcinoma of the angle of the mouth heals slowly due to wrinkling and unfolding with talking and eating. A collodion dressing may aid through fixation of the area.

Irradiated lips should be protected against freezing and shielded against blistering sunlight by a broad hat or protective salve. Jagged or misaligned teeth should be smoothed by an abrasive disc or extracted. Small superficial ulcers may heal following electrofulguration and elimination of irritation. Closure of deeper and more persistent ulcerations, and especially those recurring after previous irradiation, is expedited by surgical excision and approximation. It is particularly important that the section be carried into healthy tissue and that tension on the approximated devascularized margins be relaxed, if healing is to be secure. Tension is readily relieved by an arched traction bar. Excision of longitudinal ulcers with re-approximation of mucosa to the vermillion border has already been discussed. Excised tissue should be examined for cancer since submucosal recurrence may occur after seemingly adequate therapy. Primary surgical resection is to be considered in lesions of

the lip which are recurrent after previous intensive radiotherapy, cancers associated with destructive ulceration necessitating subsequent plastic repair and superficial linear ulcerations occurring in an atrophic light-sensitive mucosa.

CARCINOMA OF VULVA, PENIS AND ANUS

Carcinoma can be eliminated effectively from the anus, vulva and penis by irradiation, but since these areas are exposed to maceration and surface contamination, recovery from irradiation is slow and such areas are susceptible to recurrent ulcerations.

The skin of the vulva is particularly susceptible to chronic painful ulceration after radiotherapy.[2,12] Excision and electrosurgical removal of resectable cancer of the vulva saves time and trouble for doctor and patient. The ulcerated superficial carcinoma associated with leukoplakia is not suitable for radiotherapy. We have successfully eliminated inoperable vulvar lesions by low intensity interstitial radium, and with durable healing. Painful ulceration persisting following irradiation closed by simple excision and approximation recurred and a sliding flap was required for sufficient relief of tension to permit durable closure.

Papillary or superficial carcinoma of the penis can be eliminated by irradiation with minimal loss of organ tissue. Circumcision through reduction of maceration and infection lowers the incidence of trophic ulcer. In the event of recurrent ulceration after adequate radiotherapy, biopsy and electrocoagulation or excision and approximation is advised, since the lesion is most probably a trophic ulcer.

Carcinoma of the anus with infiltration of musculature has been treated by low intensity radium needles and intraluminary radium rather than by resection in

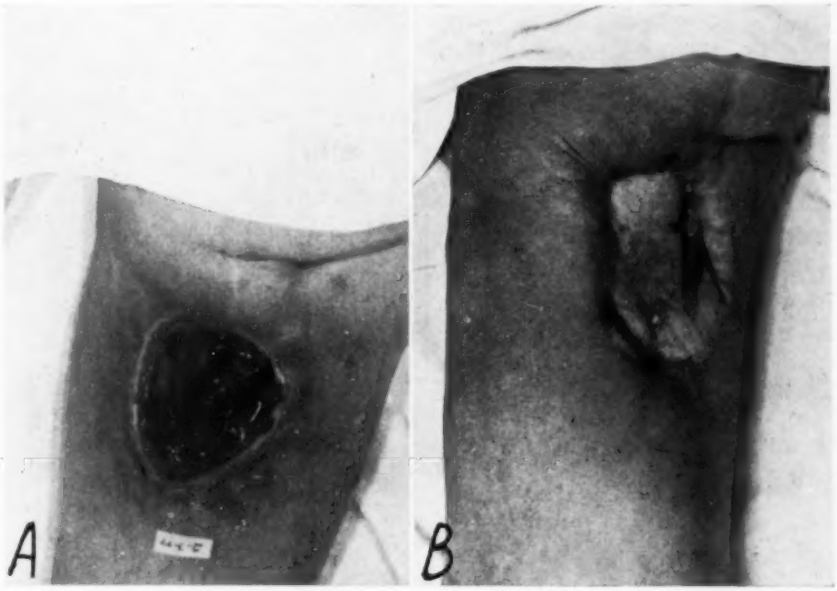

Fig. 12. Case IX. D. H., housewife, aged thirty-nine. Neurofibrosarcoma, recurrent after two resections and 3,300 r in tissue, 180 kv. roentgen therapy. Eradicated by combined radiotherapy and ulcer repaired by free split graft. *A*, necrosis 5 by 7 cm. in posterior thigh, four months after 15×225 r (3,375 r) in tissue, 180 kv. (constant), half-value layer 1.0 mm. Cu. followed by 6,060 mg-hr., 0.5 mm. Pt interstitial radium (6,000 gamma r) in five days, all delivered from August 24 to September 21, 1943. *B*, three years later. Area remains well healed after closure by free split graft. No recurrence or metastases.

FIG. 13. Case x. N. B., physician, aged 26. Elective, precautionary application of pedicle flap to forearm after 8,000 gamma r of radium and 1,600 r in tissue of 180 kv. (constant) roentgen therapy during three weeks for postoperative residual fibrosarcoma in 1942. No recurrence and skin of near normal consistency four years later.

some cases in order to preserve sphincteric function. Healing has been slow with delayed recurrent ulceration. Surface closure can be accomplished by excision and approximation with a sliding flap for relief of tension.

CARCINOMA OF SKIN LARGER THAN 5 CM.

In spite of usually good tolerance of well vascularized skin (see Case VIII)[20] an excessively large lesion may so deplete the regenerative capacity of tissue that grafting may be necessary. In Case VII closure of the extending ulceration by a sliding flap stopped recurrent extending necrosis and preserved the impaired and exposed facial nerve. Although the skin of the neck tolerates intensive radiotherapy well, delayed healing or recurrent ulceration occurs at times from blistering sunburn, from scratching or rubbing of the skin by a tight or stiffly starched collar. A patient recovering from radiodermatitis of neck should wear his collar soft and loose.

SARCOMATA

The eradication of fibrosarcoma requires administration of 7 to 10 threshold erythema doses, which when delivered into large areas of the skin may lead to persistent or recurrent ulceration with necrosis of the underlying subcutaneous tissues. Interstitial radium combined with deep roentgen therapy in this dosage has been effective in the control of five sarcomata persistent after resection and deep roentgen therapy. The large size of lesions and devascularization by previous surgery and irradiation required application of grafts for closure in 5 cases. In 3 cases grafting was delayed until considerable necrosis had occurred, while in 2 other cases precautionary grafting was elected eight weeks after completion of radiotherapy.

Osteogenic and periosteal fibrosarcoma of bone have been treated by intensive deep roentgen therapy, to be followed by amputation eight to twelve weeks later in case no metastatic lesions grew to obvious size during that interval. The program was agreed to in advance by the patient, family, surgeon and radiotherapist. In a few cases no viable neoplasm was found in multiple microscopic sections. In one case amputation was necessitated by ulceration and osteomyelitis developing two years after radiotherapy in a patient refusing amputation originally. Pathological fracture with non-union has been met in another case five years after successful control of a fibrosarcoma of the thigh by intensive deep roentgen therapy.

ELECTIVE SURGICAL CLOSURE FOLLOWING INTENSIVE RADIOTHERAPY

Precautionary surgical closure of large intensively irradiated areas permits eradication of previously uncontrolled cancer. Closure of the irradiated area by unirradiated skin provides a more durable surface, which is more comfortable and tolerates trauma without hazard of ulceration or necrosis. In the case of a young physician, Case x, irradiated for postoperative residual fibrosarcoma of the forearm, a full thickness pedicle flap from the abdomen was applied following irradiation and block resection. In Case II, multiple small deep grafts were applied to a subsiding radiodermatitis of the buttock to prevent subsequent ulceration and necrosis, which seemed certain to eventuate after delivery of 12

T.E.D. during three weeks to a postoperative residual fibrosarcoma of the buttock. A large, free, thick split graft would have given more complete coverage and a better cosmetic result, but the multiple free grafts were easily applied, took well and covered the ulcerated area effectively. The grafted central area has good consistency and sensation, while the peripheral atrophic area has only subsistent vascularity and feels itchy and uncomfortable.

DISCUSSION

Trophic ulceration is to be anticipated occasionally following proper radiotherapeutic eradication of cancer from areas of only subsistent vascularity, marginal recuperability and depleted regenerative capacity. The low healing reserve of such tissues must be conserved by individualization of therapy with attention to all constitutional, regional and environmental, as well as radiotherapeutic, factors influencing wound repair.

The total effective dosage of radiation should be the smallest which will consistently and completely eradicate cancer. The space distribution must be so regulated as to deliver a cancericidal dosage throughout the neoplasm and yet with minimal irradiation of the adjacent uninvolved tissues of the tumor bed. Attenuation of intensity and protraction of fractionation, within reasonable limits, promotes the recovery of uninvolved tissues for comparable destruction of cancer. However, even with the best regulated therapy, ulceration will occur occasionally in regions which are deficient in blood supply, directly overlying bone and cartilage, exposed to maceration and infection, damaged by recurrent trauma or extensively involved by disease. The possible desirability of subsequent surgical repair is to be anticipated in such cases. Primary surgical excision may expedite the management of certain resectable lesions associated with infection of bone or cartilage or occurring in areas exposed to maceration, subject to excessive trauma, or lacking in subcutaneous tissue.

Radiotherapy was elected rather than surgery for eradication of cancer in this reported series of cases for the following general reasons: (1) residual or recurrent neoplasm after previous surgical removal; (2) declared inoperability of lesion; (3) more certain eradication of lesion infiltrating underlying essential structures; (4) more preservation of adjacent healthy tissue; (5) probability of spontaneous healing; and, in that event (6) avoidance of hospitalization.

The weighing of probable benefits against possible hazards of irradiation, surgery and combined therapy call for an open mind, discerning judgment and courageous decision if the patient is to receive the most certain control of cancer with least subsequent disability.

SUMMARY

1. Chronic ulceration occurs following properly controlled radiotherapeutic eradication of cancer due to inadequate recuperability of tumor bed which may be (*a*) inherent from poor vascularity, malnutrition, and atrophy; (*b*) inhibited by trauma and infection with resulting necrosis; or (*c*) depleted by excessive demands of intensive therapy or extensive disease.

2. In a series of 33 cases, delayed or recurrent ulceration occurred one month to six years after initial healing in 22 cases, while in 11 cases ulceration persisted following irradiation.

3. The main factor contributing to recurrent ulceration was deficiency of blood supply due to (*a*) vessels being of small caliber and lacking deep collaterals (dorsum of hand, scalp), or (*b*) impoverishment of vascularity by previous surgery or irradiation. Ulceration resulted from infection introduced by sunburn, freezing or other trauma (lip, nose, ear, hand) and aggravated by maceration and contamination (vulva, penis, anus).

4. Chronic ulceration persisting after irradiation occurred only in case (*a*) the lesion was over 4 cm. across, or (*b*) complicated by exposure and infection of cartilage or bone.

5. The recuperability of tissues of mar-

ginal vitality must be promoted and conserved by proper nutrition, correction of anemia, conservation of regional blood supply, reduction of infection, avoidance of sunburn, freezing or other trauma. Radiation appears to conserve tissue repair when delivered at relatively low intensity, in fractionated dosage, with proper space distribution, and in dosage adequate to completely eradicate cancer by the first course of therapy. Surgical repair conserves recuperability.

6. The surgical technique of plastic repair, causes of failure and specific indications for the various procedures are presented in detail according to preparation of ulcer bed, and closure by (*a*) approximation, (*b*) sliding flap, (*c*) pedicle flap, (*d*) multiple small deep grafts, and (*e*) free split grafts.

7. The advantages of surgical repair in chronic ulceration occurring after irradiation are: (*a*) expeditious closure with prompt relief of pain and exclusion of infection, (*b*) elimination of necrotic tissue and prevention of further necrosis, (*c*) exclusion of residual neoplasm by microscopic examination, (*d*) closure by durable skin, with reduction of hazard of trauma and avoidance of malignant degeneration.

8. Surgical repair warrants consideration in the case of ulceration which fails to heal under good medical care, within three months after irradiation, or which is exposed to contamination and maceration, or is associated with infection of cartilage or bone.

9. The possible desirability of subsequent plastic repair is to be anticipated following the radiotherapeutic eradication of cancer in the case of (*a*) lesions over 5 cm. in diameter, (*b*) recurrent neoplasms previously irradiated, (*c*) lesions complicated by involvement of cartilage and bone; (*d*) lesions of the scalp, especially if over 2 cm. or fixed; (*e*) areas anatomically deficient in vascularity and exposed to excessive trauma; (*f*) areas exposed to maceration and contamination. Primary surgical resection with plastic closure warrants consideration in the initial planning of treatment in such cases.

10. Cancer was eradicated by radiotherapy rather than by surgery in this series of cases due to various reasons, such as declared inoperability, more certain eradication of infiltrating cancer, greater preservation of uninvolved tissues, and probability of spontaneous healing in most cases.

11. Precautionary surgical closure elected eight to twelve weeks following intensive radiotherapy (1) permits administration of higher total dosage for eradication of more radioresistant neoplasms, and also (2) allows elimination of larger neoplasms which so exhaust the inherent regenerative capacity of the area as to require grafting for closure.

12. Preliminary enlightenment of the cancer patient with reference to the nature of his disease, the probable response to treatment and the possible need for subsequent plastic repair develops an intelligent forbearance and cooperation which permits more adequate control of the cancer, better management of complications and avoidance of trouble and misunderstandings.

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DISCUSSION

Dr A. W. Oughterson, New York, N. Y. It is now recognized by surgeons that most of the complications encountered in the healing of wounds can be prevented if they are anticipated and proper preventive precautions are carried out. These factors may be grouped under the four headings of nutrition, blood supply, infection, and trauma as has been done. Adequate evaluation of these factors plus the newer knowledge of techniques and dosage in radiation therapy have greatly reduced the risk of ulceration in radiation therapy of tumors. Prevention of such complications is therefore the most important measure.

Chronic ulceration, however, may occur if adequate preventive measures have not been taken. In the management of ulceration as in the preventive measures the same careful attention must be given to nutrition, blood supply, infection, and trauma, in addition to those factors peculiar to the particular lesion. A second type of ulceration is that which may be inherent in the location and extent of the tumor and the treatment which may be necessary. Such instances are those tumors closely associated with bone.

Subclinical nutritional deficiencies may be of the greatest importance when heavy irradiation is necessary. It is important to correct not only such coexisting diseases as diabetes and syphilis but anemia, vitamin deficiencies, hypoproteinemia, and electrolyte balance. It may be necessary to consider the albumin and globulin fractions rather than the total proteins alone.

Tissue injured by irradiation is especially susceptible to infection, hence portals of entry for bacteria must be carefully guarded. One of the most common errors is the extraction of teeth after they have been injured by irradiation with resulting infection and osteomyelitis. Here both trauma and infection are added insults in a bone whose blood supply has already been injured.

It is well to remember that no surgical operation is bacteriologically sterile and that bacteria are always present. These ordinarily cause no trouble in the presence of the normal body defense. However, when surgery is undertaken in tissue damaged by irradiation the risk of infection is a major problem. It should be remembered that the usual boiling of surgical instruments does not destroy anaerobes. These are ordinarily phagocytized but when the blood supply is impaired in the presence of heavy scar tissue this may not occur and a low grade infection results opening the area to further infection. It is safer to autoclave all material and instruments when operating in such an area. The avoidance of unnecessary surgical trauma is also of the greatest importance. When ulceration has occurred the margin between healing and continued ulceration may be very narrow. Success or failure to obtain healing may depend on infinite pains and attention to each detail in the healing process.

Dr. L. H. JORSTAD, St. Louis, Mo. I wish to congratulate Dr. Hunt and Dr. Breit on this constructive and timely presentation of a difficult, and too often not discussed subject. That "surgery and irradiation should be considered supplementary, rather than competitive in the treatment of cancer" is particularly applicable in the more advanced cases of cancer such as are illustrated in this paper. Not only is it desirable that the radiotherapist should be familiar with the methods, principles, and possibilities of surgical treatment of chronic ulceration, but the surgeon as well should be familiar with the possibilities of irradiation in cancer, particularly in this group of cases.

I might add a general principle to those the authors have cited. I think it wise to delay major reconstructive procedures approximately one year following eradication of the extensive neoplasm, provided the functional disturbance due to the defect does not outweigh the possibility of recurrence of malignancy in the defect resultant from such eradication. This is predicated on the basis that the greater majority of recurrences occur within the first year. It discourages doctor and patient to find recurrence of malignancy in a reconstructed area of tissue.

Of course, the last paragraph and statement by the authors cites this whole problem; to wit, "The weighing of probable benefits against possible hazards of irradiation, surgery and combined therapy call for an open mind, discerning judgment and courageous decision if the patient is to receive the most certain control of cancer with the least subsequent disability." To this statement could be added "and the shortest period of disability with the minimum of discomfort."

DR. HUNT (closing). It is fitting that discussion on the subject of eradication of cancer with surgical repair of subsequent ulceration should be participated in by oncologists particularly experienced in the field of surgery. I wish to thank Dr. Oughterson for emphasizing that the fundamental processes interfering with the healing of ulceration after radiotherapy should be subjected to the same physiological analysis which is accorded ulceration following destructive agents. The problems of wound repair have received much attention in surgical literature and too little in radiological literature, considering that recovery from intensive radiotherapy always involves problems of wound repair. Also, I wish to thank Dr. Jorstad for emphasizing the desirability of generous collaboration between surgeons and radiotherapists in cancer therapy. We are inclined to apply grafts earlier than Dr. Jorstad advises, providing the dosage of radiotherapy has been adequate, ranging from 7 to 10 T.E.D., and that multiple biopsies from the ulcer base are free from cancer. The difficulties of repair become somewhat greater beyond three to six months following radiotherapy due to progressive endarteritis, fibrosis and chronic infection. Again I wish to thank Dr. Oughterson and Dr. Jorstad for their reassuring discussions.

RADIATION AND SURGICAL TRENDS IN THE TREATMENT OF CANCER OF THE CERVIX UTERI*†

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SELECTION of the subject here discussed is evidence of the greater interest which lately has fallen upon the use of surgery in the treatment of cancer of the uterine cervix. The possible trend away from the better established radiological methods is viewed by some with apprehension. It is feared that more general use of surgery will result in higher primary mortality as well as a fall in survival rates. Others look upon revival of radical hysterectomy as resuscitation of a method explored already and proved by experience to be less practical than the use of roentgen rays and radium. Another group, by no means small in number, is of the opinion that the best treatment for some patients may necessitate a combination of both surgery and radiation.

Proponents of radical hysterectomy are optimistic. By applying the many advances made in modern surgery, they have perfected their technique and proved in well selected patients that the primary mortality need be no higher for operation than for irradiation. They have emphasized the importance of selecting patients. It is not intended that surgery will replace established methods. In the treatment of certain selected groups, however, radical hysterectomy is presented as a challenge to irradiation. A provocative situation of that order can be a wholesome stimulus to clinical advance. That point is best exemplified in the well publicized work of Meigs,[9] and there can be no doubt that he has advanced the technique of radical hysterectomy to the greatest perfection that has been attained. Upon that basis there is complete justification for exploring again a procedure that once was almost entirely discarded. The operation has never been entirely abandoned, however, and interest has been supported by several individuals: notably, Bonney, of London, and Lynch, of California, and their respective associates. The modern approach to the problem is based upon experiences of these men, as well as experiences of others who have favored combinations of surgery and irradiation.

According to Berkeley and Bonney,[4] abdominal hysterectomy for cervix cancer was first proposed in 1878 by Freund. Not before 1895, however, was the feasibility of radical operation demonstrated. The same year marked the discovery of x-rays by Röntgen. Possibilities for radical operation were demonstrated by Ries in work done on dogs and in cadavers. The following year Clark and Thring independently applied the operation to living patients. Wertheim produced the clinical data that fixed his name to the technical procedure. Schauta, Adler, and many others extended knowledge of surgical treatment and attempted various modifications of technique.

Coincident with the early but steady advances in surgery were the epoch-making developments in physics, chemistry, and biology that followed the discovery of roentgen rays and radium. Robert Abbe, of New York, was one of the early pioneers in applying radium to medicine. Burnam[6] attributes to Wickham's visit to Baltimore in 1909 a stimulus to the work continued by Howard A. Kelley. A small amount of radium was then in use at Baltimore and

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they had observed a remarkable response in a patient with cervix cancer that reappeared after hysterectomy.

We of this generation may not fully appreciate the profound impressions gained in those early days from favorable responses in patients with completely hopeless prognoses. The degree of palliation must have been in sharp contrast to that which might have been expected from such commonly used methods as acetone treatment or actual cauterization. In more favorable cases the relative simplicity of treatment must have been in sharp contrast to the hazards of radical surgery.

Radiosensitivity as manifested by favorable clinical response was not the only factor in determining the adaptability of cervix cancer to irradiation. Accessibility of the lesion to palpation and visual inspection were equally as important. Difficulties encountered in attempting to eradicate the disease surgically are also to be considered. The method became firmly established by the work of such men as Henry Schmitz, Heyman, Bailey, Ward, Healy, and many others. It is not surprising that contributions to advance in radiation treatment were made by gynecologists as well as radiologists. Clinical results were of a quality that resulted in general agreement upon radiation as the method of choice for treatment of cervix cancer. The finality of that decision is well demonstrated in a letter written by H. S. Crossen[7] and published in his textbook on operative gynecology.

Irradiation is, of course, not the complete answer to the treatment of cervix cancer. Successful treatment is not gained in all of the early lesions. That has been one point upon which has been based renewed interest in surgery. To better evaluate the treatment of cervix cancer, it is necessary to consider some of the biologic properties of the disease upon an anatomical and pathological basis.

Despite origin in the same organ or type of tissue, there are wide variations in the clinical behavior of cancer in different individuals. In some instances the neoplasm may remain localized for relatively long periods. In others there may be metastases that develop promptly. Neither size of the primary lesion nor duration of symptoms is an accurate indicator of the stage of clinical advance of cervix cancer. Extensive involvement can occur with only slight enlargement of the cervix. Some early cancers form bulky cervical tumors that almost fill the vagina. Patients applying for treatment immediately after the onset of suspicious symptoms may present well advanced cancers. In others the tumor may appear clinically to be localized to the cervix in spite of symptoms present for a substantial period. Those differences are due to variations in biologic properties responsible for infiltrating tendencies and circumstances prompting dispersion by other methods.

Taylor and Nathanson[14] have published a classic study upon methods of spread of tumors. Direct infiltration of surrounding tissues takes place along fascial planes or between laminations of tissue. In cervix cancer the paths of least resistance to invasion extend laterally into the parametrial regions along the ligament of Mackenrodt at the base of the broad ligament. Infiltrations can extend in other directions including all of the paracervical tissues. Involvement of that order is more common in the anterior direction toward the bladder. Other points of extension include the sacrouterine ligaments and vaginal wall. In the latter instance, one finds occasional examples suggesting the possibility of transplant by contact.

Fascial planes between the cervix and the bladder and rectum inhibit direct invasion of those structures. Time required for tumor to traverse the few millimeters of distance to those organs is usually on the order of many months and sometimes years. The effectiveness of that barrier has caused Bonney[4] to believe that an uninvolved margin of tissue only 1/20 inch in thickness is consistent with successful surgical removal. Infiltrations extending in other di-

rections, however, do not meet with the same obstruction. Invasion into the parametrium also enters a zone traversed by the majority of blood vessels, lymphatics, and nerves. It is by means of those structures that metastases can occur.

Vascular and lymphatic structures form a plexus about the uterus which converges near the junction of the corpus and cervix. Main pathways extend lateralward along the base of the broad ligaments. Lesser lymphatic connections are made with extensions along the vagina, chiefly in its anterior wall, that communicate with a plexus near the urethral orifice. A few variable trunks pass lateralward with the ovarian vessels, or follow the sacro-uterine ligaments to the chain of sacral and aortic nodes. As noted before, the early direct extensions of cancer of the cervix are into the paracervical tissues, and adjacent portions of the cardinal ligaments. It is in those regions that contact can be made with the principal lymphatic channels. One might expect nodes most frequently involved to be those following roughly the course of the uterine vessels.

In the primary group of nodes the more constant include the ureteral gland, located near the point of crossing of the ureter and uterine artery, nodes along the iliac vessels, those at the bifurcation of the common iliacs, and the obturator group situated in the obturator fossae. Secondary nodes are found along the common iliac and sacral vessels and the aorta. Inconstant nodes may be found adjacent to the cervix and upper vagina or near the bladder and rectum. Lymphatics that follow the ovarian vessels or sacro-uterine ligaments communicate with nodes of the secondary group in the common iliac and aortic chains or with the sacral group.

Data on lymph node involvement have come from findings at autopsy and at operation. Considerable attention has been focussed upon node involvement by those who have combined irradiation with surgical procedures such as iliac lymphadenectomy. That procedure was developed in 1930 by Taussig,[13] but was also conceived independently by Leveuf.[8] The cervix and uterus are irradiated in the attempt to simplify treatment and lessen the hazard of radical operation. Upon the assumption that the quantity of radiation reaching the regional nodes is inadequate for the destruction of tumor, those regions are treated surgically by the removal of lymphatic structures. The usual sequence is to begin treatment with roentgen rays. This is followed by iliac lymphadenectomy, and radium is then applied to the cervix.

Morton[10] has pointed out the difficulty in obtaining accurate statistical information on lymph node involvement. He cites experiences of several authors. Among patients selected for radical hysterectomy, positive lymph node involvement is found in about half of those showing parametrial invasion. Positive lymph node involvement is found in about one-third, or less, of patients with the parametria microscopically free of cancer. Thickening of a parametrium may be only inflammatory, and a parametrium clinically free of invasion may contain microscopic deposits of tumor. It is obvious that findings at bimanual examination are not accurate for determining the probability for lymphatic dispersion. It can be assumed that a large percentage of patients have lymph node metastases when diagnosis is established. The first nodes most frequently involved include the obturator, hypogastric, ureteral, and sacral groups. More advanced involvement can extend to a second barrier in the lumbar and inguinal regions. The second group is involved only in advanced stages, and in not more than 5 or 10 per cent of patients does dispersion reach the second group without prior invasion of the first.

Berkeley and Bonney[4] found lymph node involvement in 40 per cent of their patients treated by radical hysterectomy. The five year survival for that group was about half the rate for patients without demonstrable metastases. Taussig[13] performed iliac lymphadenectomy chiefly in patients falling into the Stage II League of Nations

classification of clinical advance. More favorable lesions showed few positive glands. The operation was deemed impractical for more advanced cases. The nodes most commonly involved in the order of frequency were the hypogastric, obturator, ureteral, and external iliac. Of 70 patients observed for more than five years, the incidence of glandular involvement was 33 per cent. As noted by Bonney, the survival rate for patients without positive nodes was more than twice as good as that for individuals with lymphatic dispersion.

The rationale of surgery is based upon the fact that cancer beginning in the cervix remains for a variable period as a process localized within the immediately adjacent tissues. Dispersions beyond margins of direct infiltration may not necessarily preclude surgical cure. Radical hysterectomy includes removal of all nodes in the primary group as well as those along the common iliac arteries in the secondary group. The parametrial tissues and vagina are excised as widely as possible. The node excision is not a block dissection on the order of that done in the axilla for breast cancer, but succeeds in removal of the accessible glands and interruption or resection of their communicating lymphatic vessels. The operation meets, therefore, the anatomical and pathological requirements for adequate treatment. It attempts also to meet surgically some of the biologic variations in tumor growth. Among cancers that undergo metastasis promptly after onset of the disease, there is a possibility that early dispersions will be trapped in the nodes removed. Efficiency of the procedure is dependent upon the completeness of local removal and the fixed regularity at which early dispersions will follow and remain within passageways brought into the operative field. Survival rates for radical hysterectomy show that the tumor is often confined within the volume of the tissue removed. The incidence of recurrence, on the other hand, indicates the frequency with which extension or dispersion occurred outside that volume.

Berkeley and Bonney[4] report that 65 per cent of all recurrences appear within two years after operation. Ninety per cent of the total appeared by the end of the fifth postoperative year. Of considerable significance is the fact that they have not experienced a single recurrence after the tenth year. The location of reappearing cancer varied in different patients. One-fourth were located in the lower pelvis, including the vagina, bladder, and rectum. Approximately half were in the upper pelvis, including cellular tissue lateral to the uterus and bone. Less than one-fifth were behind the peritoneum in the abdomen and in the vertebrae. From these data it seems likely that some recurrences result from undetected extensions beyond margins of recognized infiltration, but that the majority are derived from dispersions beyond the zone of operative removal.

Bonney[5] reports an operability rate of 63 per cent on 112 patients with cancer of the cervix seen at Middlesex Hospital and Chelsea Hospital for Women between 1907 and 1911. From that time onward, there were others who also determined methods of treatment for patients examined at those hospitals. Bonney has used the operability value of 63 per cent to estimate the total number of patients he may have seen for selecting his operable material. It is noted, however, that among his private patients the operability rate was about 80 per cent.

Between 1907 and 1936 Bonney treated surgically a total of 500 patients. During that period it is reckoned that consultation was performed upon approximately 800 patients. There were 70 postoperative deaths, making a primary mortality of 14 per cent. The mortality was highest in the early years, and for the last 200 patients, it was only 11 per cent. The operative mortality was greatest among those with more advanced lesions.

The clinical results reported by Bonney show for the 500 patients treated surgically a five year survival rate of 40 per cent. There were 300 patients in whom no lymphatic dispersions were demonstrable. Of

that number 53 per cent were well at the end of five years. Definite lymph node involvement was found in 200 patients, of whom 22 per cent survived the same period.

A comparison of surgical results with those obtained from irradiation can be made only on the basis of a uniform type of clinical material. One method for study is utilization of all patients as they are received in a given series. By that means the average result obtained for irradiation in one clinic can be compared with the average result obtained at another, in which operable patients are treated surgically and irradiation alone used only for the more advanced tumors. A comparison can also be made by deleting the advanced cases, and selecting from irradiation results only those statistics pertaining to operable tumors. The first method is to be preferred, but in the case of Bonney's data, such a comparison is not possible. In attempting the second method one finds the work of Pitts and Waterman well suited to such a study. Due to the fact that they have followed the Schmitz classification for cancer of the cervix, it is possible to select with reasonable accuracy the operable material from published results. Statistical dataare available on a large series of patients, and for many years they have followed a particular technique using low intensity radium needles. Of some interest in comparing their data with surgical results is the fact that they are gynecologists.

The most recent publication by Waterman and his associates[16] gives absolute statistics upon 579 patients treated between 1926 and 1940. In Stage I (Schmitz) the five year survival rate was 78.2 per cent. For Stage II it was 59.2 per cent. These two groups represented one-third (34 per cent) of the total series, and together showed a survival rate of 61 per cent. For Stage III, the five year value was 28.1 per cent. If Stages I, II, and III are grouped together, then three-fourths (76 per cent) of the total series is included. For that number 43 per cent survived the five year period. The absolute value for the total of 579 patients was 33.3 per cent.

Data for comparing results are given in Table I. The 500 patients reported by Bonney are shown as 63 per cent of his total series. Survival rates in that group can be compared with clinical results in 76 per cent of Waterman's series if Stages I, II, and III (Schmitz) are included. On that basis, the five year survival rates are 40 per cent for surgery and 43 per cent for irradiation. The 300 patients without demonstrable metastases represented 37.5 per cent of Bonney's total of 800 patients. Among those there was a five year survival of 53 per cent. Stages I and II (Schmitz) represented 34 per cent of Waterman's series. Those patients may be assumed to have been relatively free of lymph node metastases, and 61 per cent survived the five year period. The 200 patients with positive nodes in Bonney's series represented one-fourth of his entire series. Experience in that group might be expected to

TABLE I

CLINICAL STATISTICS REPORTED BY BONNEY AND BY WATERMAN. A COMPARISON OF SURGICAL AND IRRADIATION RESULTS IN SPECIFIED PERCENTAGES OF TOTAL CLINICAL MATERIAL

	Classification	Per Cent Total	Five Year Survival Per Cent
Bonney 800 patients	Operable 500 patients	63	40
	Negative nodes 300 patients	37	53
	Positive nodes 200 patients	25	22
Waterman 579 patients	Schmitz Stages I, II, III 442 patients	76	43
	Stage I, II 197 patients	34	61
	Stage III 245 patients	42	28

parallel roughly the results obtained in Stage III (Schmitz), which included 42.3 per cent of Waterman's series. In those patients the five year survival rate for surgery was 22 per cent, and for irradiation 28.1 per cent.

Comparison should be made also with the results reported by Meigs.[9] Patients for surgical treatment have been selected carefully from among those with early lesions. An operability rate on the order of 10 to 15 per cent is anticipated. The reasons for choosing surgery in the treatment of those patients are based upon his experiences with certain early tumors found to be resistant to radiation. Hysterectomy eliminates the cervix as a potential focus of recurrence. Lesser amounts of damage to bowel are to be expected for surgical treatment. Finally, Meigs believes that tumor dispersions to lymph nodes cannot be destroyed by irradiation. By the end of 1945 radical hysterectomy had been done upon 91 patients without a single operative death. Thirty-six patients had been followed for a period of three years, with a survival rate of 77.7 per cent. Upon the basis of Bonney's work, one might expect that approximately 80 per cent of the recurrences to be expected would have occurred by the end of the third year. Due to Meigs' careful selection of patients, however, it is quite possible that an even greater percentage of the total recurrence rate will have developed by that time. For that reason his five year end results may not be particularly different for those found at the end of a three year period. In Waterman's report the results for 1936 to 1940 were given separately to show advance in clinical work. For those years, Stages I and II represented 31 per cent of the clinical material. Among that number the five year survival was 71 per cent. That comparison can be seen in Table II.

On the basis of statistics that have been compared, there is not shown for surgery any marked superiority in clinical results. One of the important reasons given for surgery is that by removal there may be eradication of lymphatic dispersions which might not be destroyed by irradiation. Lymph node metastases affect adversely the prognosis in cancer of the cervix. Among patients with node involvement proved by radical hysterectomy or iliac lymphadenectomy, the survival rates are only half those obtained in patients without demonstrable metastases. In Bonney's experience 60 of every 100 operable cases were without positive nodes. He contends, therefore, that survival rates of 60 per cent must be shown for irradiation before that procedure can be considered practical for those patients. That point in question is not so easily determined due to the fact that it is impossible to predict on clinical examination the exact status of regional nodes. If, on the other hand, one considers Stages I and II (Schmitz) as representing operable material, then the value stipulated by Bonney is exceeded in statistics reported by Waterman.

Taussig[13] compared results among 70

TABLE II

CLINICAL STATISTICS REPORTED BY MEIGS AND BY WATERMAN. A COMPARISON OF SURGICAL AND IRRADIATION RESULTS IN SPECIFIED PERCENTAGES OF TOTAL CLINICAL MATERIAL.

	Classification	Number of Patients	Three Year Survival Per Cent	Five Year Surviva Per Cent
Meigs	Operability 10–15 per cent	36	77.7	
Waterman	Stage I, II (Schmitz) 31 per cent	62		71

iliac lymphadenectomies with 118 Stage II (League of Nations) patients treated during the same period with radiation alone. The five year survival for patients with gland dissection was 38.6 per cent. For radiation alone the value was 22.9 per cent. He commented upon advance in methods of radiation treatment, and anticipated an improvement in results. Of considerable significance is the fact that by including more recently treated patients not then observed for a period of five years, there was noted a decrease in the incidence of positive nodes. The value among his first 70 patients was 33 per cent. For his entire series the incidence was 26.8 per cent. Effect of irradiation on lymph node involvement is shown also in the detailed study made by Morton.[10] Among his patients treated by iliac lymphadenectomy or radical hysterectomy 39.3 per cent showed positive nodes. Following the use of preoperative irradiation the incidence dropped to 11.4 per cent. Those experiences establish for irradiation a definite effect upon tumor in the regional nodes.

Neither Morton nor Taussig was able to demonstrate in tissues removed at iliac lymphadenectomy any constant histopathologic changes attributable to radiation effect. The fall in incidence of positive nodes after preoperative irradiation may not represent permanent destruction of cancer. The effects of roentgen rays applied through pelvic fields have been studied by repeated biopsies taken from the cervix.[1] Marked changes occur, but even in the few that show clinical disappearance of tumor, the effect is only temporary. Additional treatment by radium is necessary for permanent destruction of the lesion. It is obvious, therefore, that external irradiation alone is not apt to control tumor in lymph nodes. The contribution from radium to regional tumor-bearing points varies with the amount and technique of treatment.[2] Nolan and Quimby[12] have shown by calculation that a better distribution of radiation is obtained by combining intrauterine tandems with interstitial sources introduced into parametrial and paracervical tissues. The use of low intensity radium needles is undoubtedly an important factor in the excellent clinical results obtained by Pitts and Waterman. From data on lymphatic involvement, there can be no doubt that some survivals after irradiation occur in patients with positive nodes.

There is no reason for viewing with apprehension the greater interest being manifested in surgery for the treatment of cancer of the cervix. Further exploration is justified on the basis of advance that has been made in operative procedures. The use of surgery in conjunction with radiation treatment is also important for accumulating data upon the changes produced by roentgen rays and radium on lymph node metastases. Nathanson[11] has recently described an extraperitoneal approach to iliac lymphadenectomy that may simplify the operation and increase the number of nodes accessible to removal.

It is well known that some cervix cancers display surprising resistance to irradiation despite the presence of rather favorable stages of clinical advance. There is no method for predicting accurately the degree of radiosensitivity to be expected for a given tumor. It is possible that classification made on the basis of gross characteristics of the tumor may be of value. Cervix cancers can be divided into infiltrating and everting types.[3] By correlating gross appearance with histopathologic type, and estimations of tumor age with duration of clinical symptoms, methods may be devised for better evaluation of biologic properties. Those researches should also be correlated with data on lymph node metastases. It is not improbable that certain infiltrating types will be found to have biologic properties for which radical hysterectomy will be a valuable adjunct in treatment.

Despite the fact that a rising trend in surgery need not be viewed with apprehension, mention of risks involved cannot be escaped. Over-popularization of radical hysterectomy can result in injudicious use of the operation. Meigs has emphasized the

task involved in perfecting technique for radical hysterectomy. It should also be pointed out that knowledge of surgery alone is not adequate for the care of patients with cervix cancer. There must be knowledge of radiation effects and the biologic properties of tumor growth. Adequate treatment is particularly important in the more favorable stages of clinical advance due to the possibility for good results in that group. If thought is directed toward care of patients over a wide geographical area, it is more practical to populate regions with talent for satisfactory radiation treatment. Upon that basis there is strong argument for adherence to better established radiological methods.

It is not to be implied that radiation treatment is a simple procedure without hazard. There is risk in under-exposure and in over-irradiation. Inadequate treatment results in persistent tumor more resistant to radiation. Over-exposure can produce untoward sequelae by damage to normal tissues. There may be severe injury to the bowel and the bladder. Importance of the tumor bed as a normal structure is often neglected in clinical practice. Tod[15] has described "supralethal" effects of radiation in which destruction of the tumor bed can result in uncontrolled growth of cancer by removal of normal inhibitory mechanisms. Responses of that order are sometimes incorrectly interpreted as evidence of marked resistance to radiation. It is not unreasonable to believe that the average treatment employed for cervix cancer has produced favorable results in spite of over-exposure. The normal tissues in question seem to have a relatively high tolerance to damaging effects of radiation. Average methods of treatment, however, cannot be expected to equal the clinical results that have been quoted for comparing radiological and surgical statistics. Neither can the surgeon with only occasional opportunity for performing radical hysterectomy expect to equal results obtained by those particularly skilled in the procedure. A point of value, perhaps unanticipated in the greater interest in surgery, is the challenge radical hysterectomy presents in the treatment of early lesions. That provocative situation is stimulating. Advance in radiology has equalled in importance that made in surgery. It is essential that knowledge of that advance be more generally applied in clinical practice. It is the duty of those who combine radiation with surgery to produce knowledge of radiation effects on lymph node metastases. It is the duty of all of those who employ radiation to seek more data upon the biologic properties of tumor growth.

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DOSAGE DETERMINATION WITH RADIOACTIVE ISOTOPES

II. PRACTICAL CONSIDERATIONS IN THERAPY AND PROTECTION*

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INTRODUCTION

A KNOWLEDGE of radiation dosage from artificially radioactive substances deposited in tissue is important in applications of these materials to tracer studies, as well as in therapy. In employing tracers in humans, it is essential to know that the incidental irradiation does not exceed safe limits. In all tracer work it must be assured that the radiation itself does not affect the phenomenon being investigated. While this can actually be determined only by trial, a knowledge of the tissue doses involved is useful. In therapy the same considerations apply as in any other type of irradiation.

It is highly desirable to express these doses in terms of roentgens, since that unit is generally employed for the usual types of radiation therapy with x-rays and radium. In the case of x-rays, ionization measurements in phantoms give satisfactory dosage data. For radium and radon in sealed containers, extensive dosage tables have been calculated, based on an experimentally determined value of radiation from a standard point source. Similar methods would be applicable to any gamma ray emitting radioactive substance *enclosed in a sealed container and used in the same manner as radon.*

As commonly used, most radioisotopes are ingested or injected in soluble form and subsequently deposited with a greater or less degree of selectivity in various cells or organs. It is evident that neither measurements nor calculations of the types cited would be satisfactory under such conditions. Nevertheless when the physical factors of half life and radiation energy, and the physiological factors of uptake and excretion are known, it is possible, in some cases at least, to make satisfactory estimates of tissue dosage.

The roentgen, as defined by international agreement, applies only to x- or gamma radiation; it can therefore be used for gamma ray emitting isotopes but not for radiation due to primary beta particles. (The roentgen is defined as "that quantity of x- or gamma radiation such that the associated corpuscular emission per 0.001293 gm of air, produces, in air, ions carrying 1 e.s.u. of quantity of electricity of either sign.")

On the other hand if the energy absorbed per gram of air per roentgen ($\sim$83 ergs) is made the unit of energy absorption for beta rays it is possible to establish a comparable basis for beta ray dosage. To be sure, in going from air to tissues certain corrections will have to be made because the energy absorption in tissue per roentgen exposure of x- and gamma rays depends on both tissue composition and radiation wavelength, but in practice, for soft tissues, these corrections are not very large. Hence it is possible to define an "*equivalent roentgen*" as "that amount of beta radiation which, under equilibrium conditions, releases in one gram of air as much energy as one roentgen of gamma rays." Since the accepted symbol for the roentgen is "r," it is convenient to designate the equivalent roentgen by "e.r." (This is essentially the same unit as the "rep" or "roentgen equivalent physical" of the Plutonium Project.)

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In the present paper, formulae expressing the relationship between radiation dose and isotope concentration are developed and their clinical applications discussed. Since it is felt that the mathematical derivations will be of less interest to many readers than the practical aspects, the paper has been divided into two parts. The development of formulae will be left to Part II. In Part I, some of the final expressions will be presented, together with tables containing a considerable amount of pertinent information. Examples of the applications of the formulae to specific isotopes and definite problems will also be given in this section.

PART I. PRACTICAL ASPECTS

I-A. *Beta ray emitters.* When a radioisotope emits only beta rays, the dose is essentially confined to the regions containing the material because the range of the beta particles in tissue is only a few mm.* The *total dose* D_β, *in equivalent roentgens*, due to the complete disintegration of a radioelement biologically stable and present in a uniform concentration of C microcuries per gram of tissue is (see Part II-A)

$$D_\beta = K_\beta C \text{ e.r.} \qquad \text{I}$$

where

$$K_\beta = 88\overline{E}_\beta T \text{ e.r. per } \mu\text{cd}\dagger/\text{gram} \qquad \text{Ia}$$

T is the half life of the isotope in days and $\overline{E}_\beta$ the *average* energy per disintegration of the beta rays in million electron volts (Mev).

Doses per hour and per day are respectively

$$\begin{aligned} d_h \text{ (hour)} &= D_\beta f_h \\ d_\beta \text{ (day)} &= D_\beta f_d \end{aligned} \qquad \text{II}$$

where f_d and f_h are the fractions of the entire quantity of the isotope which disintegrate per hour or per day respectively. Values of T, $\overline{E}_\beta$, K_β and f_d are given in Table 1 which refers to beta ray emitters. Z is the atomic number and A the atomic weight of the elements given in the first column. The last column gives the ranges in water for the most energetic beta particles of each beta ray spectrum for the different isotopes. Detailed discussion of this table will be given below. It should be noted that the column for K_β gives immediately the dose in equivalent roentgens for each microcurie completely disintegrating within a gram of tissue.

I-B. *Gamma ray emitters.* When a substance is a gamma ray emitter, the problem of dosage determination is more complicated. The rays released in a given gram of tissue produce only a small amount of ionization there; most of their energy is expended elsewhere along their paths. The problem becomes somewhat analogous to that of interstitial radium gamma ray dosage, except that instead of discrete sources one is confronted with extended ones.

The *total dose* D_γ due to gamma rays emitted by the complete disintegration of a radioelement biologically stable and present in a uniform concentration of C microcuries per gram of tissue is given by (see Part II-B).

$$D_\gamma = K_\gamma C g \text{ roentgens} \qquad \text{III}$$

where

$$K_\gamma = 1.44 t I_\gamma \times 10^{-3}. \qquad \text{IIIa}$$

The dose delivered in one day is

$$d_\gamma \text{ (day)} = D_\gamma f_d \qquad \text{IV}$$

f_d having the meaning expressed above. K_γ expresses the number of roentgens at 1 cm distance in air due to the *complete disintegration* of an unfiltered point source of one microcurie; $1.44 \times t$ is the average life in hours, I_γ the dose-rate in roentgens per hour at 1 cm in air from an unfiltered point source of 1 mc. The quantity g in equation III is a *geometrical factor* depending on the size and shape of the tissue mass under con-

* Many organs in small animals used in experiments dealing with isotopes emitting high energy beta-rays are not small in comparison to the range of the beta particles. Proper estimate of the dose in these instances is, in general very complicated, and must be left to the future.

† μcd.—microcuries destroyed, i.e., microcuries remaining in the tissue until completely disintegrated.

TABLE I

Physical data pertaining to calculations of radiation dosage resulting from beta rays and/or very soft x-ray radiation. The values of K_β and S_β are based on uniform and biologically stable concentrations of radioelements distributed in tissues of linear dimension large as compared to the range of the beta particles. The sign "0" under the heading "Radiation" indicates the absence of nuclear gamma rays.

$\overline{E}_\beta$ is the average energy per disintegration.

$K_\beta = 88\overline{E}_\beta T$ is the radiation dose expressed in equivalent roentgens due to beta rays emitted during the complete disintegration of 1 μc of radioelement per gram of tissue.

$f_d = (1 - e^{-0.693/T})$ is the fraction of the entire quantity of isotope which disintegrates in 24 hours.

$S_\beta = \dfrac{0.1}{K_\beta \times f_d}$ is the concentration of radioisotope expressed in μc/kg which will deliver a dose of 0.1 e.r. to tissue during the first 24 hours of exposure.

Element	Z	A	Radiation	T Half life in days	$\overline{E}_\beta$ (Mev)	K_β e.r./μcd per gram	f_d fraction disintegr. per day	S_β μc per kg	Weight per mc in 10^{-9} gram	Maximum range in water (mm)
Group A: $\overline{E}_\beta$ is known to an accuracy of a few per cent										
C	6	11	β^+, 0	0.014	0.380	0.47	1.0	213	0.0012	4.2
N	7	13	β^+, 0	0.007	0.475	0.29	1.0	345	0.0007	5.6
Na	11	22	β^+, γ	1100	0.225	22000	$6.3 \cdot 10^{-4}$	7.3	197	2.1
		24	β^-, γ	0.61	0.540	29	0.68	5.1	0.113	6.4
P	15	32	β^-, 0	14.5	0.695	885	0.047	2.4	3.6	8.0
Cl	17	38	β^-, γ	0.026	1.390	3.2	1.0	31	0.0076	27
K	19	42	β^-, γ	0.515	1.395	63	0.74	2.1	0.167	19
Sc	21	46	β^-, γ	85	1.117	870	0.008	14.3	30	1.0
V	23	48	β^+, K, γ	16	0.175	245	0.042	9.7	5.9	2.8
Mn	25	52	β^+, K, γ	6.5	0.085	48	0.101	20.6	2.6	2.2
		56	β^-, γ	0.108	0.890	8.5	0.998	11.8	0.046	14
Fe	26	59	β^-, γ	47	0.120	496	0.015	13.4	21.3	1.5
Co	27	56	β^+, γ	85	0.655	4900	0.008	2.6	36.6	7.0
		60	β^-, γ	1940	0.099	17000	$3.6 \cdot 10^{-4}$	16.5	895	0.8
Cu	29	61	β^+, K, 0	0.142	0.433	5.4	0.992	18.7	0.067	5.5
		64	β^+, β^-, K, 0	0.53	0.120	5.6	0.73	24.4	0.26	2.6
Zn	30	63	β^+, K, γ	0.027	0.965	2.3	1.0	43.5	0.013	12
As	33	76	β^-, γ	1.12	1.170	115	0.46	1.9	0.655	15.7
Br	35	82	β^-, γ	1.5	0.150	20	0.37	13.5	0.95	1.6
In	49	114	β^-, (γ)	50	0.940	4150	0.014	1.7	44	9.4
I	53	130	β^-, γ	0.525	0.270	12.4	0.73	11.0	0.53	4.5
		131	β^-, γ	8.0	0.205	144	0.083	8.3	8.1	2.2
RaE	83	210	β^-, 0	4.85	0.330	141	0.133	5.3	7.85	5.2
Group B: $\overline{E}_\beta$ is less accurately known than $\overline{E}_\beta$ in Group A										
C	6	14	β^-, 0	$1.7 \cdot 10^8$	0.05	$8 \cdot 10^8$	$4 \cdot 10^{-7}$	32	$18 \cdot 10^4$	0.24
S	16	35	β^-, 0	88	0.055	420	0.0079	30	24	0.2
Ca	20	45	β^-, (?)	180	0.10	1580	0.0039	16	62	0.8
Sr	38	89	β^-, 0	55	0.57	2760	0.013	3	38	7
		90	β^-, 0	9000	0.22	$17 \cdot 10^4$	$8 \cdot 10^{-5}$	8	6200	2.2
Y	39	90	β^-, 0	2.6	0.90	200	0.24	2	18	11
Sb	51	124	β^-, γ	60	0.66	3480	0.012	2.4	57	12.3
I	53	128	β^-, γ	0.017	0.77	1.2	1.0	87	0.017	9.8
Au	79	198	β^-, γ	2.7	0.32	76	0.23	5.7	4.1	3.8
Group C: $\overline{E}_\beta$ includes the total localized x-radiation following decay by electron capture										
Mn	25	54	K, γ	310	0.0054	147	0.0022	340	128	
Fe	26	55	K, γ	1500	0.0059	780	$4.6 \cdot 10^{-4}$	280	633	
Co	27	58	β^+, K, γ	65	0.035	20	0.012	415	29	1.5
Zn	30	65	β^+, K, γ	250	0.01	180	0.003	185	124	1.2
Group D: $\overline{E}_\beta$ consists of part of the radiation released in the decay by electron capture										
Y	39	86	K, γ	105	0.005	46	0.007	310	69	
In	49	111	K, γ	2.7	0.0058	1.4	0.23	310	2.3	0.01

sideration and on the absorption of the gamma rays; in dosage tables for interstitial radium a factor analogous to g is implicit. For *radon* filtered by 0.5 mm Pt, I_γ in equation IIIa would correspond to the well known figure of 8.4 r per mc-hr (or mr/μc-hr) at 1 cm distance in air, and $K_\gamma = 133 \times 8.4 \times 10^{-3} = 1.1$ r per μcd. The values of I_γ and K_γ together with other pertinent information for gamma ray emitting radioisotopes are given in Table II.

I-C. *Safe tracer concentration.* In the main Tables I and II are self explanatory. Attention should be directed to column 7 in

TABLE II

Physical data pertaining to calculations of radiation dosage resulting from gamma rays. The sign "0" under the heading "Radiation" indicates the absence of nuclear gamma rays. The column headed "Annihilation Radiation" refers to positron-electron recombination, the column headed "Nuclear Gamma Radiation" refers to gamma rays originating in the disintegrated nucleus. The numbers in parentheses indicate the number of photons of the particular energy that are released per disintegration. In Group B, the numbers in square brackets pertain to x-ray emission following electron capture.

I_γ is the exposure in roentgens at 1 cm distance in air from an unfiltered point source of 1 mc, for one hour; or milli-roentgens per microcurie-hour (see formula XIV).

$K_\gamma = 1.44 I_\gamma \times 10^{-3}$ is the number of roentgens at 1 cm distance in air from an unfiltered point source, per microcurie destroyed.

$f_d = (1 - e^{-0.693/T})$ is the fraction of the entire quantity of isotope which disintegrates in 24 hours. (T is the half life in days.)

Element	Z	A	Radiation	t Half life in hours	E_j in Mev: Annihilation radiation	E_j in Mev: Nuclear gamma radiation	$I\gamma$ at 1 cm. mr/μc-hr r/mc hr	$K\gamma$ at 1 cm r/μc-hr	f_d fraction disintgr. per day
Group A: elements not decaying by electron capture, or x-ray emission following electron capture so soft that it can be treated like beta radiation and hence making no significant contribution to $I\gamma$									
C	6	11	β^+, 0	0.33	0.511(2)		6.2	0.003	1.0
N	7	13	β^+, 0	0.17	0.511(2)		6.2	0.0015	1.0
Na	11	22	β^+, γ	26500	0.511(2)	1.30(1)	13.2	500	$6.3 \cdot 10^{-4}$
		24	β^-, γ	14.7		1.38(1) 2.76(1)	19.1	0.40	0.68
Cl	17	38	β^-, γ	0.62		1.6(0.36) 2.15(0.47)	7.6	0.0068	1.0
K	19	42	β^-, γ	12.4		1.51(0.25)	1.95	0.035	0.74
Sc	21	46	β^+, γ	2040		0.90(1) 1.12(1)	11.4	33.5	0.008
V	23	48	β^+, K, γ	384	0.511(1.16)	0.98(1) 1.33(1)	16.3	9.0	0.042
Mn	25	52	β^+, K, γ	156	0.511(0.7)	0.736(1) 0.94(1) 1.46(1)	19.5	4.4	0.101
		56	β^-, γ	2.59		1.77(0.3) 2.06(0.2)	9.4	0.035	0.998
Fe	26	59	β^-, γ	1128		1.1(0.5) 1.3(0.5)	6.55	10.7	0.015
Co	27	56	β^+, γ	2040	0.511(2)	0.845(1) 1.26(1)	17.95	37.2	0.008
		60	β^-, γ	46500		1.16(1) 1.32(1)	13.5	900	$3.6 \cdot 10^{-4}$
Cu	29	61	β^+, K, 0	3.4	0.511(1.56)		4.8	0.024	0.992
		64	β^+, β^-, K, 0	12.8	0.511(0.38)		1.2	0.022	0.73
Zn	30	63	β^+, K, γ	0.65	0.511(1.96)	0.96(0.09) 1.90(0.04)	6.9	0.0065	1.0
As	33	76	β^-, γ	26.8		0.55(0.37) 1.20(0.12) 1.75(0.01)	2.2	0.083	0.46
Br	35	82	β^-, γ	36		0.547(1) 0.787(1) 1.35(1)	15.1	0.79	0.37
Sb	51	124	β^-, γ	1440		0.6(1) 1.7(0.5)	7.9	16.4	0.012
I	53	128	β^-, γ	0.42		0.428(0.07)	0.2	0.00012	1.0
		130	β^-, γ	12.6		0.416(0.55) 0.537(1) 0.667(1) 0.744(1)	13.05	0.237	0.73
		131	β^-, γ	192		0.080(1) 0.307(1)	2.65	0.735	0.083
Au	79	198	β^-, γ	65		0.40(1)	2.4	0.22	0.23
Group B: elements with x-ray emission following electron capture whose contribution to $I\gamma$ is not negligible									
Mn	25	54	K, γ	7450		0.835(1) [0.0054(1)]	4.9+[11]	52	0.0022
Fe	26	55	K, γ	36000		0.07(2 · 10^{-3}) [0.0059(1)]	[10]	—	$4.6 \cdot 10^{-4}$
Co	27	58	β^+, K, γ	1560	0.511(0.3)	0.805(1) [0.0064(0.85)]	5.7+[7]	12.8	0.012
Zn	30	65	β^+, K, γ	6000	0.511(0.03)	1.14(0.46) [0.008(0.90)]	3.0+[5]	26	0.003
Y	39	86	K, γ	2530		0.908(1) 1.89(1) [0.0142(1)]	14.4+[3.1]	52.5+[10.3]	0 007
In	49	111	K, γ	65		0.173(1) 0.247(1) [0.0231(1)]	2.3+[1.4]	0.22+[0.13]	0.23

Table 1, headed S_β, which indicates the "*safe tracer concentration*," that is, the number of μc per kg of *tissue* weight which will result in a whole tissue dose of 0.1 r the first day, *due to the beta rays alone.* (The gamma ray contribution will be discussed below.) In the case of a short-lived element, the dose on succeeding days will quickly decrease to the vanishing point, while for long-lived substances it will continue at an appreciable level for some time.*

I-D. *Distribution of the radiation in tissue.* The physical data presented enable the experimenter to calculate the actual dose delivered to a tissue or individual whenever the isotope concentration C is known as a function of time (see Part II-D). This depends on the amount of isotope administered, the species and metabolic state of the test animal, the mode of administration, the chemical form under which the radioelement is given, etc.

Physiological information of this nature

* This criterion of "safe dose" is decidedly conservative. One might prefer to choose such a level as 1 r in 10 days or some other value based on a longer period of time. This might avoid complications due to various half lives. However, the present familiar idea of safety is based on daily dose, hence that has been used here. It is not to be assumed that larger tracer doses should never be administered. It is sometimes entirely justifiable to use considerably higher doses in diagnostic problems.

is of great importance; the literature shows that a good deal of animal work has been done on the relative uptake of various isotopes by different tissues at different times. As an example, in Figure 1 are shown the relative radiation doses delivered in different tissues in mice injected intraperitoneally with P^{32} in the form of Na_2HPO_4 (16). The animals were sacrificed at various times after the administration of the material, and the concentration of P^{32} was determined for the various tissues and organs. With this information it was possible to calculate the dose of radiation received by each tissue as a function of time. Similar calculations were made for the whole body assuming uniform distribution. The "theoretical" whole animal dose* after complete disintegration of the isotope, was taken as 100 per cent, and all other tissue doses referred to this value. Thus at the end of three weeks, 64 per cent of the theoretical complete dose had been delivered; but all tissues tested, except the bone, had received already practically all their radiation because most P^{32} had disappeared. The liver, for example, had received about 33 per cent of the theoretical uniform dose. At

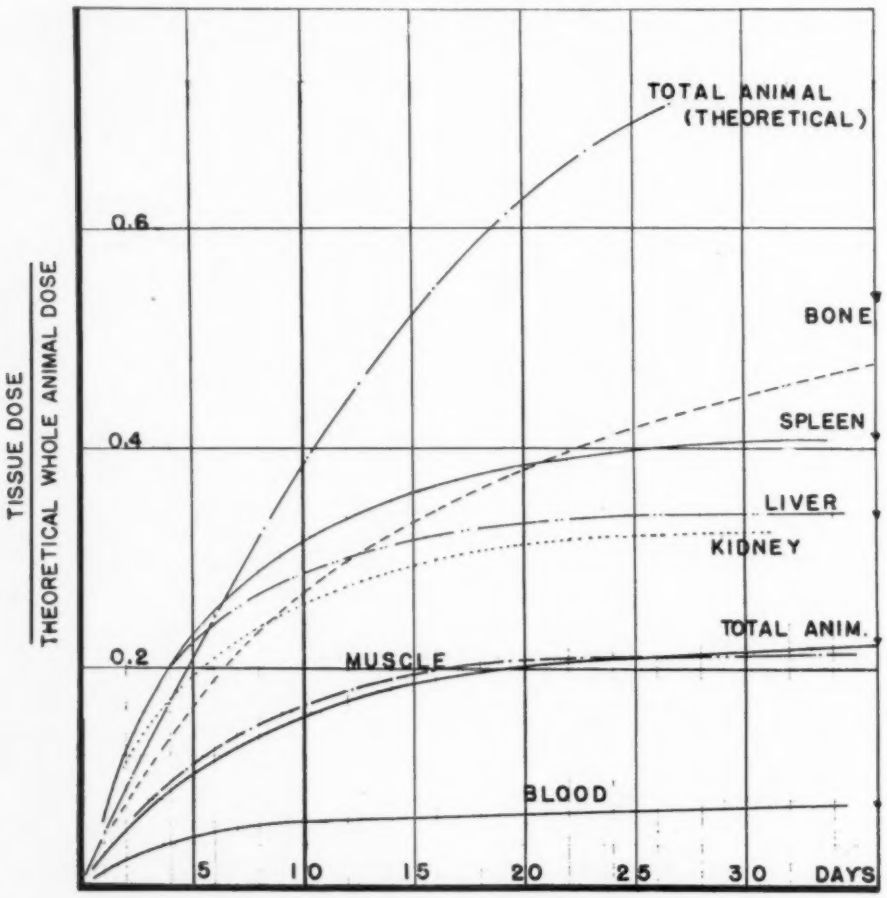

FIG. 1. Radiation dosage due to the beta-ray activity of P^{32} in different tissues in mice as a function of time. The points marked on the right margin are the actual tissue doses obtained by extrapolation to infinite time. Theoretical whole animal dose equals K_β times the number of microcuries administered divided by the total weight of the animal.

* By "theoretical" whole animal dose is meant the dose D_β which would have been obtained in the animal after complete disintegration of the isotope on the assumption of uniform concentration in the animal and of total lack of biological elimination.

that time the bone had received 39 per cent; but in the bone the dosage increased to 48 per cent at the end of 36 days.

No tissue actually attained the theoretical dose or would have attained it after longer periods of time because of biological elimination. From the curves, the actual tissue dosage per μc of P^{32} thus administered in a mouse of 25 grams can now be calculated. The total animal concentration would be 0.04 μc/gram and the "theoretical" total animal dose $D_\beta = K_\beta \times 0.04 = 885 \times 0.04 = 35.4$ e.r. (K_β from Table 1). The liver, then, at the end of three weeks would have received 33 per cent of this value or 12 r; similarly the bone at 36 days would have had $0.48 \times 35.4 = 17$ r.

It is recognized that with P^{32} in mice these determinations are not as accurate as one would wish because the linear dimensions of most organs are smaller than the range of a considerable portion of the beta particles emitted by P^{32}. Similar information in larger animals would yield more reliable figures. Conversely this type of calculation would be fairly accurate even in a small animal, as the mouse, if soft beta ray emitters (H^3, C^{14}, S^{35}, etc.) were used.

When working with humans it is not possible in general to study concentrations throughout the body and their variations with time by *in vivo* measurements; the extreme concentration of iodine in the thyroid is an exception. For most isotopes information must be obtained from biopsy and autopsy measurements and hence the data are meager; moreover they are scattered through various publications which were often not prepared with this point in mind. Accordingly it has happened too often that the published results lack some essential fact, such as the actual weight of the individual. It is to be hoped that more of this information will be forthcoming. In the meanwhile, it is wise to adopt a conservative attitude in dealing with humans whenever physiological information is lacking. This can be done by assuming that no biological elimination takes place.

I-E. *Differential absorption ratio.* To take into account the differences in uptake which lead to differences in dose for the various tissues, it is convenient to express the concentration in terms of a "differential absorption ratio" (D.A.R.). For any tissue, this is the ratio of concentration of an isotope in that tissue to the average concentration in the body (neglecting excretion). Thus under the assumption just made if a particular tissue has a D.A.R. of 1, it receives the same dose of radiation as the average of the whole body. On the other hand, if it has a D.A.R. of 10, it receives ten times as much radiation as the average.

In calculating the safe doses for tracers, it is highly desirable to have some idea of the *range of the D.A.R.'s*. The safe dose is assumed to be 0.1 r per day for the entire body; if a certain tissue has a D.A.R. of 10, it would have received 1 r while the rest of the body received 0.1 r. This might lead to undesirable irradiation of certain tissues or organs from a dose believed safe otherwise.

The procedure outlined above needs clarification. In general, single tissues and the whole body have different rates and modes of elimination, hence the tissue D.A.R. will vary with time. The question then arises as to the time at which D.A.R.'s have significance in determination of tissue dosage. Evidently the D.A.R. will be too low when taken too soon after the isotope administration because the concentrations have not yet stabilized. Likewise adoption of the D.A.R. after several half lives will have little or no significance because most of the isotope has disintegrated. One useful index, whenever the isotope reaches the body tissues through the circulatory system, could be the stabilization of the plasma concentration. No general rule, however, can be given and good judgment is of paramount importance.

I-F. *Effective half life.* In instances of extreme concentrations as in the case of *radioiodine* I^{131} *administered to humans* in the form of KI or NaI, greater accuracy can be obtained. It will be noted that the formula I for the dose, D_β, contains the half life of the element. If the amount of

iodine in the gland decreases both by decay and by excretion, the *effective half life* will be less than the physical. Such effects can be determined only by actual measurements. In this particular problem, counts are made at intervals with a Geiger counter in a fixed position over the thyroid gland. If there were no excretion of the material from the gland, these counts should decrease exactly in accordance with the physical decay curve for the iodine; that is, for I^{131} they should be at half their initial value

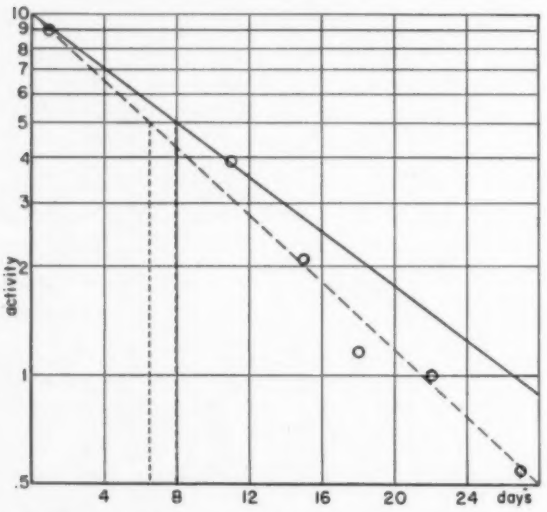

FIG. 2. Solid line: physical decay curve of I^{131}; half life 8 days. Broken line: actual decay curve of I^{131} in a hyperthyroid patient; effective half life 6.5 days.

after 8 days, one-fourth at 16 days, etc. Actually, they decrease exponentially but more rapidly. Figure 2 shows the actual range of counts, in one patient treated with I^{131} for hyperthyroidism. The physical decay curve for the material is shown as a heavy line. It is obvious that the decrease was appreciably faster than this. The average "effective half life" in this case is 6.5 days (broken line). It is evident that the use of this number instead of 8 in equation I results in a decrease of 19 per cent in the administered dose, an amount which is probably clinically significant in therapeutic work. It would be now possible to calculate from formula I the dose delivered under normal conditions if the initial concentration C were known. This can be determined either by actual biopsy or "guessed" by estimate of the gland weight and measurements of the radioactive content of the gland by proper *in vivo* observations.

It is evident from Table 1 that the actual amounts of the *safe concentrations in tissue* do not vary very greatly; it must be realized that the intervals at which they can be repeated do. A reasonable interval between full tracer doses of any particular element would be four or five half lives, unless the material has been shown to be excreted fairly completely in a shorter period. If no significant excretion occurs, a tracer of Na^{24} could be repeated within about three days, while P^{32} should not be repeated in less than about 2 months, and Ca^{45} not before two years have elapsed.

It should be mentioned in this connection that the safe doses listed here are calculated on the assumption that the individual is receiving no radiation from any other source. Extensive radiographic or fluoroscopic procedures may result in an appreciable dose of radiation, and such possibilities must not be overlooked.

I-G. *Tracer Isotopes—Examples.* In order to illustrate the use of the material presented in this paper sample calculations will be given for some isotopes commonly used in tracer experiments and in therapy. These will be presented in order of the complexity of their spectra.

A) *Radioactive Phosphorus—*P^{32}*—(Beta particles only)*

If the isotope were evenly distributed throughout the body and no elimination took place the values of Table 1 would be directly applicable. Thus, if 2.4 μc/kg gives a dose of 0.1 e.r., an initial radiation dose of d e.r. per day will require a concentration x μc per kg such that

$$2.4 : 0.1 = x : d$$

namely:

$$x = \frac{2.4 \times d}{0.1} = 24 \times d \ \mu\text{c/kg}.$$

If a total radiation dose D_β (e.r.) is to be given to a tissue, the concentration in that tissue should be such that

$$D_\beta = K_\beta C \text{ or } C = \frac{D_\beta}{885} \mu c/\text{gram}.$$

As already mentioned, the most exhaustive information on the distribution of this isotope in mice (16) shows that the highest radiation dose is given to bone, followed in order by spleen, liver, kidney, muscle and blood. In general, the limited information on adult humans obtained for the major part from autopsies of leukemic patients (3, 4, 5, 10, 20, 26), does not contradict the results in mice, provided that only non-infiltrated tissue obtained from patients given single doses of P^{32} be taken into consideration. Limited data on non-irradiated surgical material are also available (28). The most reliable D.A.R.'s on bone are of the order of unity though wide variations are noted not only among individuals but also among portions of the same bone (4, 28). The absolute value of the D.A.R.'s for human bone—as in the case of mice—seems to bear no detectable relation to the time elapsed between administration and assay; this points out to a slow "net" elimination of P^{32} from bone.

The highest D.A.R. reported on human marrow (10, 28) *devoid of leukemic infiltration* can also be taken of the order of unity for the first few days following P^{32} administration. Data on sternal aspiration (10), however, are decidedly lower, being much closer to that of blood. (Cf. Table VI loc. cit.). The latter in humans, receives "apparent" doses of the order of 20% of the theoretical whole body dose (13). It seems therefore that doses of the order of 2.4 μc/kg of body weight can be safely administered, though they may produce wholly transitory but definite biological effects. Such reactions have been reported by Low-Beer and Treadwell for concentrations of 6–9 μc/kg (29).

If P^{32} is administered intravenously in *insoluble form* (9) the deposition in the liver and spleen is likely to be very marked. These authors report 80–89% in the liver (dog and mouse); if this were to obtain in humans the D.A.R. would be:

$$\text{D.A.R.} = \frac{\dfrac{\mu c \text{ in liver}}{\text{liver weight}}}{\dfrac{\mu c \text{ administered}}{\text{body weight}}} = \frac{0.89 \times 70}{1.7} = 36.7$$

1.7 kg being the weight of the average human liver (12). In this case the maximum permissible concentration would be

$$\frac{2.4}{36.7} = 0.066 \mu c/\text{kg of body weight}$$

or a total tracer dose of $0.066 \times 70 = 4.6$ μc of P^{32} for a 70 kg man.

B) *Radioactive Strontium—Sr^{89}—(Beta particles only)*

Work on animals (18) indicates that this isotope is *highly concentrated in the bone.* Human material has been reported by Treadwell et al. (25) following intravenous injections. Their data point to a maximum D.A.R. in the epiphysis of bone of 13.2, and an unweighted average of 8.3 for bone, mostly in young subjects. A trend of D.A.R. change with time is not apparent. On the basis of this, the tolerance concentration would be

$$\frac{S_\beta}{8.3} = \frac{3}{8.3} = 0.4 \mu c/\text{kg of body weight.}$$

C) *Radioactive Calcium—Ca^{45}—(Beta particles only)*

The relative concentrations of this isotope in human tissue have not been reported to date. Work on mice shows that the D.A.R. for Ca in animal bone is approximately twice as that for Sr (18). Hence, if this ratio holds also for humans one should expect a D.A.R. of about $8.3 \times 2 = 16.6$.

It follows from Table 1 that the tolerance concentration would be

$$\frac{15.8}{16} = 1.0 \mu c/\text{kg of body weight.}$$

It should be noted that if calcium were

totally deposited in the human skeleton and the distribution were uniform the D.A.R. would be 10 (wt. of skeleton = 10% of body weight); nevertheless, the most active parts of the bone concentrate it more and hence the higher value adopted is not unreasonable.

It may be argued that on the basis of energy absorption in bone, the tolerance concentration just calculated for P^{32}, S^{89} and Ca^{45} could be increased by a factor of three because the energy absorbed per 0.1 r exposure in bone in the usual therapeutic x-ray range has been shown to be of the order of three times the energy absorbed per 0.1 e.r. of beta rays (21, 22). It is felt, however, that in view of the proximity of bone to marrow and of the long range of the beta rays involved, this may increase the energy absorbed in marrow to a value higher to that obtaining under body exposure of 0.1 r x-rays.

D) *Radioactive Sodium—Na^{24}—(Beta and gamma radiation)*

This isotope of sodium, administered orally or intravenously, is eliminated in very small amounts during times comparable to its half life. Since it is distributed rather uniformly throughout the body, computation of beta ray dosage can be made on the basis of D.A.R. = 1 (7, 8). The factor S_β of Table 1 can be applied directly in the case of small animals where the beta rays account for most of the radiation dose, the factor g in the gamma ray formula being very small. For larger animals and humans, however, the gamma ray contribution cannot be neglected. In this case dosage calculations become more involved.

As pointed out above the contribution of gamma rays to the daily tissue dose is $d_\gamma = C\ K_\gamma f_d\ g$ roentgens where

C = concentration in μc per gram of tissue
K_γ = roentgens at 1 cm per μcd
f_d = fraction of atoms destroyed in one day
g = geometrical factor which is a function of the size and shape of the tissue volume and the penetration of the radiation.

For purposes of calculation one may assume that the human trunk is a cylinder of radius $R = 20$ cm and height $2Z = 60$ cm, and that C is constant throughout. Under these conditions the highest dose is delivered at the midpoint of the axis and g can be expressed with sufficient approximation (Part II-B) as $g = 314 - 4140\mu$ where μ is the absorption coefficient of the gamma rays in tissue. For the gamma rays from sodium (see Table II and Fig. 5) the values of μ are 0.0296 and 0.0233 per cm respectively. An average $\mu = 0.025$ may be assumed for the present calculation and hence $g = 210.5$. Substituting for K_γ and f_d the values from Table II one obtains:

$d_\gamma = 0.40 \times 0.68 \times 210.5\ C = 58.0\ C$ r per day at the center of the trunk if C is given in μc per gram of tissue.

Similarly (Table 1):

$d_\beta = 29 \times 0.68 \times C = 19.7\ C$ e.r. per day if C is given in μc per gram of tissue.

Hence the total dose for the first day is $d_{\beta+\gamma} = 77.7\ C$. The total dose $D_{\beta+\gamma}$ can be obtained from this figure. Since 68 per cent of the atoms disintegrate during the first day, 77.7 C is 68 per cent of the total dose. Hence

$$D_{\beta+\gamma} = \frac{100}{68} \times 77.7 = 114C \text{ e.r.}$$

For the tolerance dose of 0.1 r/day,

$$S_{\beta+\gamma} = \frac{0.1}{77.7} = 0.0013 \mu\text{c per gram}$$

or 1.3 μc per kg of body weight.

E) *Radioactive Sodium—Na^{22}—(Beta and gamma radiation)*

The computation of tolerance dose follows closely that illustrated for Na^{24} except for the numerical values involved. Thus, $K_\gamma = 500$; $f_d = 6.3 \times 10^{-4}$; $g = (314 - 4140 \times 0.032) = 181$, since μ can be considered to be 0.023 for the purpose of this approximation.

Hence,

$d_\gamma = 500 \times 6.3 \times 10^{-4} \times 181 = 57\ C$ at the center of the trunk and

$d_\beta = 22{,}000 \times 6.3 \times 10^{-4} \times C = 14C$

$d_{\beta+\gamma}=71C$ e.r. per day if C is in μc per gram of tissue.

$D_{\beta+\gamma}=11.3\times10^4\ C$ e.r.*

$$S_{\beta+\gamma}=\frac{0.1}{71}=0.0014\mu\text{c per gram}$$

$=1.4\mu$c per kg of tissue or body weight

since C is considered constant throughout the body.

These two sodium isotopes offer a good illustration of the point made above regarding the repetition of tracer doses. Although the doses of the two isotopes which will give 0.1 e.r. the first day are essentially the same, the total dose from this amount of Na^{22} is much greater on account of its much longer half life and should not be repeated without careful knowledge of its excretion from the body. Conversely, the test dose of Na^{24} may be repeated much sooner.

F) *Radioactive Potassium—K^{42}—(Beta and gamma radiation)*

Under the same assumptions of distribution and elimination as in the case of Na^{24}, $K_\gamma=0.0348$, $f_d=0.739$ and $g=198$.

$d_\gamma=0.035\times0.74\times198\times C=5.2\ C$ at the center of the trunk

$$d_\beta=63\times0.74\times C=46.5C$$

hence $d_{\beta+\gamma}=51.7\times C$ e.r. per day (C in μc per gram)

$$D_{\beta+\gamma}=70C\text{ e.r.}$$

and finally

$$S_{\beta+\gamma}=\frac{0.1}{51.7}=1.9\mu\text{c per kg of body weight.}$$

G) *Radioactive Iodine—I^{130}—(Beta and gamma radiation)*

The distribution of radioiodine in the body is characterized by a *high and relatively stable deposition in normal thyroid tissue* and a low concentration in the rest of the body.

Assays in rabbits and rats (19) show that at various times after administration of iodide, most known radiosensitive tissues show average concentrations of the isotope close to that of blood. Unfortunately no information is available for the marrow. The concentration in thyroid tissue, however, is so markedly different from the rest of the body that the dosage problem assumes different aspects according to whether tracer studies or radical therapeutic procedures are contemplated. Full discussion of the latter is outside the scope of the present paper. In the case of tracer studies it is of interest to calculate merely the dose to the thyroid itself, since it is very unlikely that the radiosensitivity of any other tissue in the body is such as to overcome the very large thyroid D.A.R. From Table I the beta ray daily dose is readily calculated

$$d_\beta=12.4\times0.73\times C=9.1\ C.$$

For the calculation of d_γ, from Table II $K_\gamma=0.237$; $f_d=0.73$. The geometrical factor g is very different from the cases of sodium and potassium when the whole body dosage was considered. The usual gland (about 25 grams) can be considered made up of two separate spheres of radius equal to only 1.4 cm and for this calculation we may neglect the influence of the radiation from one lobe on the other. In this case $g=4\pi(1-e^{-\mu R})\sim 4\pi R=17.6$ since μR is very small. It follows that

$d_\gamma=0.237\times0.73\times17.6=3.0\ C$ at the center of the lobe. Hence

$d_{\beta+\gamma}=(3.0+9.1)\ C=12.1\ C$ e.r. per day, C being in μc per gram of thyroid weight.

$D_{\beta+\gamma}=16.6$ C e.r.

$$S_{\beta+\gamma}=\frac{0.1}{12.1}$$

$=0.0083\mu$c per gram of thyroid weight.

For a 25 gram thyroid this would mean $0.0083\times25=0.2$ μc of I^{130}.

* This dose ($D_{\beta+\gamma}$) would be delivered over a period of years if there were no excretion of the sodium. However, experimentally the material has a physiological half life of the order of one month or less, in normals and in individuals with congestive heart failure (24). In these cases the actual $D_{\beta+\gamma}$ is nearer to 3,000 C. For nephrotics excretion is very much slower, the biological half life may even approximate the physical, and the dose of radiation be correspondingly larger.

H) *Radioactive Iodine—I^{131}—(Beta and gamma radiation)*

Following the same pattern

$$d_\beta = 144 \times 0.083 \times C = 12C$$

and $d_\gamma = 0.735 \times 0.083 \times 17.6 = 1.1\ C$ at the center of the lobe; hence

$d_{\beta+\gamma} = 13.1\ C$ e.r. per day if C is in μc per gram of thyroid weight.

$D_{\beta+\gamma} = 158C$ e.r. (If there is no elimination.)

Therefore

$S_{\beta+\gamma} = 0.0076$ μc per gram of thyroid and for a 25 gram thyroid this would mean 0.19 μc of I^{131}.

These doses, which deliver 0.1 r to the gland and only 1 per cent of this to the entire body, are obviously well below the accepted tolerance dose to the *whole* body. They correspond to oral or intravenous administration of 0.2 to 2 μc per patient (to account for excretions of 10 to 90%), and are sufficient for excretion studies as well as for assay of surgical biopsy material. They are, however, insufficient for radioautography with thin tissue sections, for extended studies of blood concentrations and for *in vivo* investigations of iodine retention by thyroid tissue by means of external counter measurements.

Studies on blood concentration and *in vivo* measurements would require doses of the order of 5 to 20 times those calculated (thyroid doses of 4 to 15 r in about three weeks, if I^{131} is used, taking into account elimination by the organ, and only 1/10 of that amount in two days in the case of I^{130}). Autoradiographic material can be obtained only with minimal concentrations of the order of several μc per gram of thyroid tissue (15). It seems therefore that in benign conditions, doses permitting excretion and tissue assays, blood concentration and *in vivo* measurements can be expected to produce no untoward effects, since the radiation is limited for a relatively short time to a very small part of the body which is not particularly radiosensitive. However, in the case of radioautographs, when radiation therapy or total thyroidectomy is not contemplated, every effort should be made to obtain them with the fastest film and low photographic density (15).

At this point it should be brought out that when tracer studies are to be carried out once or a few times on an individual, for diagnostic purposes, the physician may legitimately employ doses considerably in excess of those giving only the radiation permitted for continuous exposure. The diagnostic radiologist does not hesitate to give local exposures of several roentgens, and to repeat these at need. The justifiable dose in such cases must be determined by the clinician responsible for the patient.

The above examples illustrate the fact that no general statement can be made regarding the relative importance of the beta- and gamma ray contributions to dosage. In the first place, the relative amount of energy emitted in the form of beta and gamma rays varies from one isotope to another. Also the geometrical factor g, which is a function of both penetration of radiation and size of organ, is likely to vary tremendously with the problem, as in the cases of sodium and iodine. This matter is discussed further in Part II where a formula is given for an approximate determination of the ratio of gamma ray dose to beta ray dose.

PART II. FUNDAMENTAL FORMULAE

II-A. *Beta ray and positron emitters.* One of the present authors published, in 1942, a preliminary paper on the determination of tissue doses from beta ray emitters (13). In order to correct some typographical errors in two of the formulae, and for the convenience of the reader, the fundamental relation of equivalence between concentration of beta ray emitters in tissue and radiation dose will be reproduced here.

Consider a mass of tissue, of linear dimensions large as compared to the range of ordinary beta particles, in which a radio element is concentrated uniformly and is not being eliminated. It is obvious that, except for regions close to the boundary of the

mass, the energy D_β absorbed per gram of tissue will be

$$D_\beta = n\overline{E}_\beta \times 10^6 \text{ ev} \qquad \text{V}$$

where $n = C/\lambda$ is the number of radioactive atoms per unit mass and $\overline{E}_\beta$ is the average beta ray energy per disintegration in Mev. Now $n = 3.7 \times 10^4 \times C/\lambda$ where C is the concentration in μc* per gram (or mc/kg) and λ the decay constant of the element in sec^{-1}.

Strictly speaking, D_β cannot be expressed in the same terms as the energy absorbed per gram of tissue per roentgen of x-rays since the latter depends on the composition of the tissue and on the wave length of the radiation. However, if one chooses as the unit the energy E_r absorbed per gram of *air* when the latter is exposed to one roentgen of radiation, this ambiguity is formally circumvented and D_β can be expressed in equivalent roentgens (e.r.). (See introduction.) From the definition of the roentgen, it follows that

$$E_r = N_a \times W = 1.62 \times 10^{12} \times 32.2$$
$$= 5.22 \times 10^{13} \text{ ev} \qquad \text{VI}$$

where $N_a = 1.62 \times 10^{12}$, the number of ions formed in a gram of air per roentgen and $W = 32.2$ ev, the energy required to produce one pair of ions in air. It follows from V and VI that D_β can be expressed in equivalent roentgens by simple division, namely

$$D_\beta = \frac{3.7 \times 10^{10}\, C\overline{E}_\beta}{5.22 \times 10^{13} \times \lambda} \text{ e.r.} \qquad \text{VII}$$

This expression can be modified into one more easily remembered if C is retained in μc per gram (or mc/kg) and $\overline{E}_\beta$ in Mev, but T, the half life of the isotope, is expressed in days.
Since

$$T = \frac{0.693}{\lambda \times 8.64 \times 10^4} \text{ days},$$

equation VII becomes

$$D_\beta = 88\overline{E}_\beta TC = K_\beta C \text{ e.r.} \qquad \text{I}$$

where

$$K_\beta = 88\overline{E}_\beta T \text{ e.r. per } \mu\text{cd/gram of tissue.} \qquad \text{Ia}$$

From this formula others can be easily derived. Thus, for any interval of time t the dose d_β would be proportional to the fraction of atoms disintegrated during that time, namely

$$d_\beta(t) = D_\beta(1 - e^{-0.693t/T}) \text{ e.r.} \qquad \text{VIII}$$

For $T > 5$ days, equation VIII can be written with an approximation of better than 1 per cent as

$$d_\beta = 61\overline{E}_\beta C \text{ e.r. per day.} \qquad \text{IX}$$

Similarly for $T > 5$ hours

$$d_\beta = 2.54\overline{E}_\beta C \text{ e.r. per hour.} \qquad \text{X}$$

Equation VIII is particularly useful in computation of the concentration necessary to deliver the so-called *tolerance dose of 0.1 r per day;* then $t = 1$ in order to get the dose for the first 24 hours. Thus, if S_β is defined as the concentration necessary to deliver the tolerance dose, it follows that

$$0.1 = K_\beta S_\beta (1 - e^{-0.693/T}).$$

By defining

$$f_d = (1 - e^{-0.693/T})$$

it follows that

$$S_\beta = \frac{0.1}{K_\beta f_d}. \qquad \text{XI}$$

Values of K_β, f_d and S_β have been presented in Table 1 (Part I A).

The values of $\overline{E}_\beta$ were calculated as outlined in a previous paper by two of the present authors (14).* It is to be realized that $\overline{E}_\beta$ depends on the disintegration scheme of the isotope under consideration

* By microcurie of any radioactive element is understood that quantity that disintegrates at the rate of 3.7×10^4 atoms per second.

* In the paper referred to (14) are given references for the disintegration schemes of a large number of isotopes. A supplementary list of references, for additional isotopes considered in Tables I and II, is appended to the main bibliography of the present paper.

and that the latter is often complex. Some are established with satisfactory accuracy and constitute the Group A of Table 1; those which are not yet very well known comprise Group B. Of these Sr^{90} is of particular interest since it decays into Y^{90} which is also a radioactive element (17). The given values of $\bar{E}_\beta$ in Group C of Table 1 include the total localized x-radiation following the decay by electron capture. The x-radiation of the elements in this group is so soft that the resulting ionization is limited to a few mm of tissue. $\bar{E}_\beta$ in Group D consists of that part of the radiation released by electron capture, which is available as Auger electrons and soft L-radiation. These last two groups are discussed in some detail in Section II C.

II-B. *Gamma ray emitters.* The determination of the dosage due to gamma radiation, originating from a stable distribution of a radioelement in a tissue, is greatly facilitated by the calculation of the constant I_γ which *expresses the exposure in roentgens at 1 cm distance from an unfiltered unit point source in air during unit time interval.* I_γ can be determined by calculating the ionization produced in a cc of air by the point source under the conditions stated above.

Let

P_j = the number of gamma rays of energy E_j emitted per disintegration

N_e = the number of electrons per 1.293 mg of air (3.89×10^{20})

σ_a = the scattering absorption coefficient per electron (Compton)

τ = the photoelectric absorption coefficient per electron

σ_p = the pair production coefficient per electron

m_0c^2 = rest energy of the electron.

On account of the Compton, photoelectric and pair production processes, a gamma ray of energy E_j will convert, per electron of air, a fraction μ_j^e of its energy into kinetic energy of secondary electrons, namely:

$$E_j\mu_j^e = E_j(\sigma_a+\tau)_j + (E_j-2m_0c^2)(\sigma_p)_j.$$

In free air, if a spherical shell of 1 cm radius and thickness dr cm. has at its center a point source of 1 mc* of an isotope emitting a gamma ray of energy E_j in a fraction P_j of its disintegrations, that shell will receive energy at the rate

$$dF_j = 3.7\times10^7\, P_jN_eE_j\mu_j^e dr \text{ (ev/sec)}.$$

The rate of energy absorption δF_j per cubic centimeter (1.293 mg.) of air under standard conditions is:

$$\delta F_j = \frac{3.7\times10^7}{4\pi}\times P_jN_eE_j\mu_j^e \text{ (ev/cc/sec)}.$$

Absorption of this energy will result in ionization, the measure of which in e.s.u. of current, is given by

$$(i_\gamma)_j = \frac{\delta F_j}{n_i\times W} = \frac{3.7\times10^7\, N_e}{4\pi n_i W} P_jE_j\mu_j^e \qquad \text{XII}$$

where $n_i = 2.08\times10^9$ is the number of ion pairs per e.s.u. of current, $W = 32.2$ ev is the energy per ion pair formed in air. From the definition of the roentgen it follows that equation XII expresses numerically the exposure in roentgens per second at 1 cm distance from a point source of 1 mc emitting P_j gamma rays of energy E_j per disintegration. A more convenient formula results if the hour is chosen as the unit of time and E_j is expressed in Mev. Formula XII then becomes

$$(i_\gamma)_j = 6.14\times10^{25}\, P_jE_j\mu_j^e \text{ r/hr/mc at 1 cm distance in air.} \qquad \text{XIII}$$

A plot of $(i_\gamma)_j$ as a function of E_j (for $P_j=1$) is shown in Figure 3. If the isotope has a complex spectrum of gamma rays of different energies E_j, each type emitted with probability P_j then XIII becomes $I_\gamma = \sum_j (i_\gamma)_j$, namely

$$I_\gamma = 6.14\times10^{25} \sum_j P_jE_j\mu_j^e \text{ r/hr/mc at 1 cm distance in air.} \qquad \text{XIV}$$

The knowledge of the constant I_γ permits the prompt measurement in milli-

* 1 mc = 3.7×10^7 disintegrations per second.

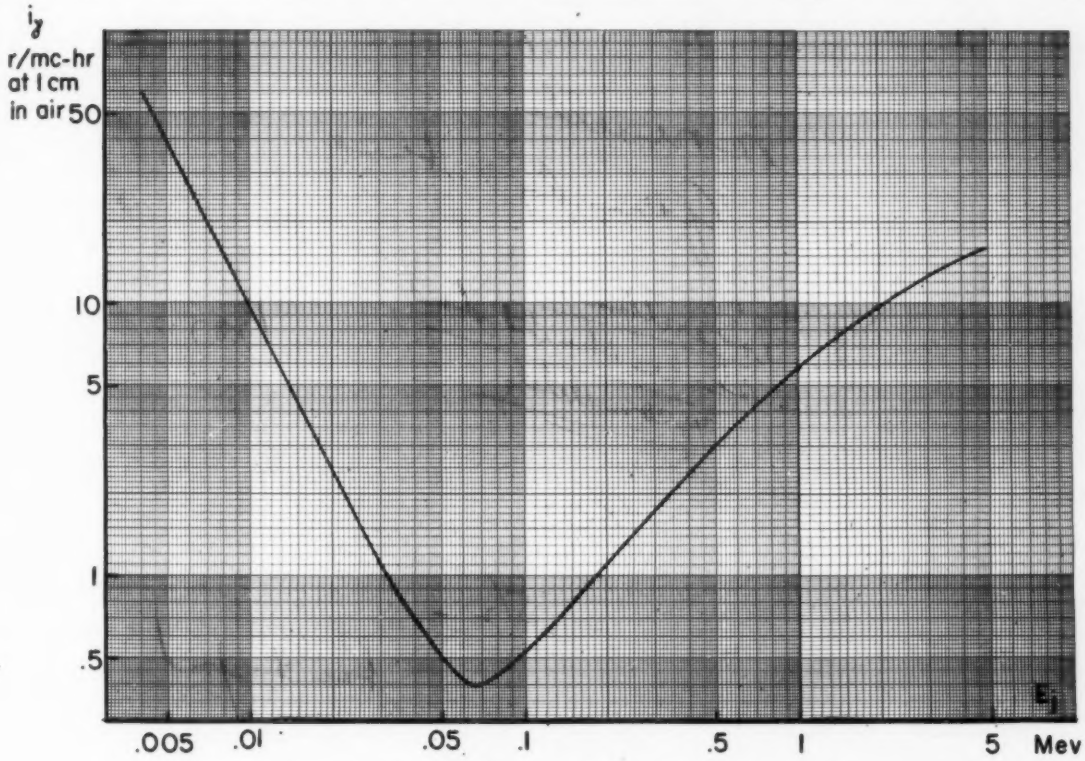

FIG. 3. i_γ in roentgens per mc-hour at 1 cm distance in air, as a function of the gamma-ray energy E_i in Mev.

curies of some gamma ray emitting isotopes, by the simple measurement of the dosage rate in roentgens. This constant is furthermore indispensable for the knowledge of therapeutic doses administered by discrete sources of known millicurie content.*

When the radioelement, by virtue of ingestion, injection, etc., is distributed throughout a tissue such as is represented by the volume V in Figure 4, with a concentration of c mc per gram, the dose rate per hour at any point O due to the quantity cdV of isotope present at a point Q, ρ cm distant from O, will be:

$$\delta d_\gamma = \frac{I_\gamma c e^{-\mu\rho}}{\rho^2} dV \text{ r/hour} \qquad \text{XV}$$

where μ is the absorption coefficient of the radiation per cm of tissue.† More precisely

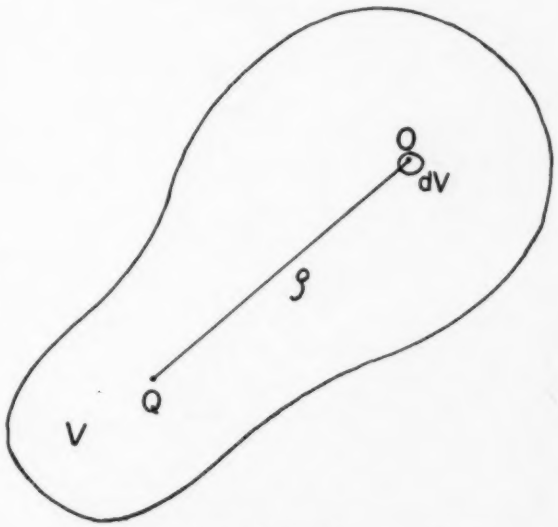

FIG. 4. Volume V with a concentration of C mc per gram.

* It should be kept in mind that a positron-emitter is always a gamma ray source, because of the annihilation radiation, even if there is no nuclear gamma radiation.

† The linear absorption coefficients μ, μ_j and the electronic absorption coefficient μ_j^e used in this paper do not include that portion σ_s of the total absorption coefficient which relates to the scattered radiation of the Compton process. This procedure is entirely justified for a few cm of water (27) and introduces no appreciable error for at least 8 cm of Al, when the radiation is of hardness comparable to the gamma rays of radium (6).

for a complex spectrum, instead of $I_\gamma e^{-\mu\rho}$ one should have $\sum_j (i_\gamma)_j e^{-\mu_j \rho}$ where μ_j is the absorption coefficient for the gamma ray of energy E_j.

If the isotope is present in a uniform and biologically stable concentration of c mc per gram the *total dose rate at point O* due to the isotope in the whole tissue is

$$d_\gamma = I_\gamma c \int_V \frac{e^{-\mu\rho}}{\rho^2} dV \text{ r/hr.} \qquad \text{XVI}$$

For the sake of brevity the integral

$$\int_V \frac{e^{-\mu\rho}}{\rho^2} dV$$

will be called the *geometrical factor* g. This coefficient must be calculated in each instance and it is exceedingly complex for non-uniform distributions.

For therapeutic dosage and protection estimates it is more convenient to evaluate the total dose D_γ per microcurie destroyed (μcd)

$$\underline{D_\gamma = 1.44 t I_\gamma 10^{-3} Cg = K_\gamma Cg \text{ roentgens}} \qquad \text{III}$$

where

$$\underline{K_\gamma = 1.44 t I_\gamma 10^{-3}} \text{ roentgens per } \mu\text{cd at 1 cm in air} \qquad \text{IIIa}$$

in which t is the half life of the isotope *in hours* and C the concentration in μc per gram.

The dosage for the first day is obviously

$$d_\gamma \text{ (day)} = K_\gamma \; C \, g \, f_d \text{ roentgen per day}$$

where

f_d is the fraction of atoms disintegrating per day. The dosages per hour are

$$d_\gamma \text{ (hour)} = I_\gamma 10^{-3} Cg \quad \text{for } t > 5 \text{ hr}$$

$$d_\gamma \text{ (hour)} = K_\gamma Cg f_h \quad \text{for } t < 5 \text{ hr}$$

where, as stated before, f_h is the fraction of atoms disintegrated per hour.

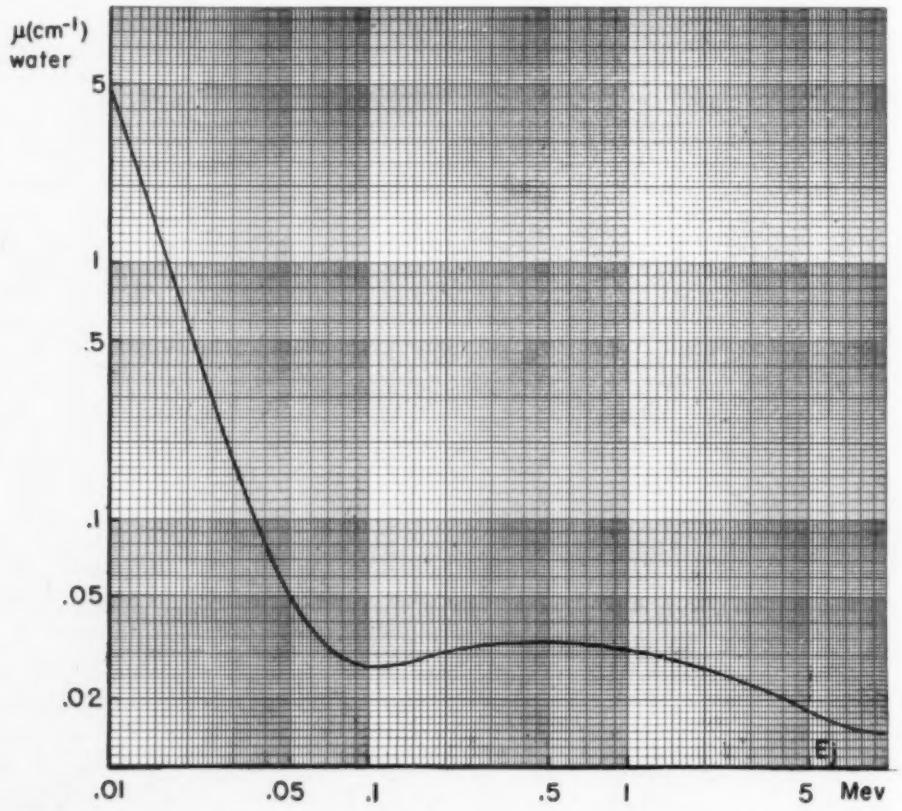

FIG. 5. Linear gamma-ray absorption coefficient μ_j in water as a function of the gamma-ray energy E_j. (μ_j includes only the absorption caused by the liberation of photoelectrons, Compton electrons and electron pairs, but not that fraction due to Compton scattering.)

The values of $K_\gamma = 1.44\ t\ I_\gamma \times 10^{-3}$ have been presented in Table II. In this table the dose due to the annihilation radiation (two gamma rays of 0.511 Mev each per positron emitted) resulting from positron-electron recombination is included in the values given for K_γ. The values of the linear absorption coefficient μ_j in water (not including Compton scattering), as a function of the gamma ray energy E_j are plotted in Figure 5.

For the sake of the illustrations presented in Part I-G the *geometrical factor* g* will be evaluated for the center of a sphere of radius R and for the midpoint of the axis of a cylinder of radius R and height $2Z$.

In the first case for the *center of the sphere*,

$$g = \int_0^R \frac{4\pi\rho^2 d\rho}{\rho^2} e^{-\mu\rho} = \frac{4\pi}{\mu}(1 - e^{-\mu R}) \qquad \text{XVII}$$

Since μ is of the order of 0.03 for most gamma rays (Fig. 5),

$$g = \frac{4\pi\mu R}{\mu} = 4\pi R$$

will be correct to within a few per cent for values of R as large as 10 cm.

For the cylinder, at the point O on its axis as indicated in Figure 6

$$g = 4\pi \int_0^Z \int_0^R \frac{r dr dz}{r^2 + z^2} e^{-\mu\sqrt{r^2+z^2}}.$$

This expression is not directly integrable, but a fair approximation may be obtained by expanding the exponential term in a series and using only the first two terms:

$$e^{-\mu\sqrt{r^2+z^2}} = 1 - \mu\sqrt{r^2+z^2} + \mu^2 \frac{(r^2+z^2)}{2!} - \cdots$$

hence,

$$g = 2\pi \left\{ Z \log_e \left(1 + \frac{R^2}{Z^2}\right) + 2R \tan^{-1}\left(\frac{Z}{R}\right) - \mu\left[Z\sqrt{R^2+Z^2} - Z^2 + R^2(\log_e [Z + \sqrt{R^2+Z^2}] - \log_e R)\right] \right\}.$$

* Note that g can be calculated for only one point at a time and it is a function of its coordinates.

For

$$Z = 30 \text{ cm and } R = 20 \text{ cm} \quad g = 314 - 4140\mu.$$

It should be realized that this approximation is justified only for relatively small values of $\mu\sqrt{R^2+Z^2}$

In general a rough estimate of the ratio of D_γ to D_β at the *center of a spherical tissue* of radius R can be readily obtained by the formula

$$\frac{D_\gamma}{D_\beta} = \sum_j \frac{P_j E_j (1 - e^{-\mu_j R})}{\overline{E}_\beta}. \qquad \text{XVIII}$$

This expression follows from taking the ratio of D_γ, as expressed by the equations III, IIIa, XIV and XVII to D_β as in equation I and by taking $\mu_j(\text{cm}^{-1}) = n_e \mu_j^e$ where $n_e = 3.007 \times 10^{23}$, the number of electrons per gram of air. Equation XVIII, therefore, applies strictly only to a mass of tissue having unit density and the same atomic composition as air.

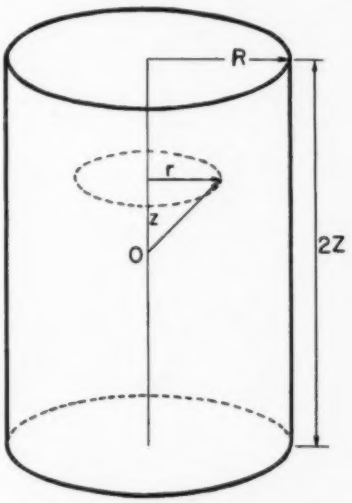

FIG. 6. Cylinder of radius R and height $2Z$.

II-C. *Decay by electron capture.* The decay by electron capture presents a special case in dosimetry since it is followed by fluorescent radiation (K, L, etc.) and emission of Auger electrons. A rigorous determination of D_β and D_γ would require a precise knowledge of fluorescent yields ω_K, ω_L which is not always available (2). For

the purpose of this paper, however, some simplification of the problem is justified. The fluorescent quanta available have in general low energy and they are absorbed in small thicknesses of tissue. Ninety-five per cent of 9 kv radiation, for example, is absorbed within 5 mm of tissue; therefore fluorescent radiation of this voltage or lower can be treated in the same manner as beta radiation of comparable range.

Of the elements listed in Tables I and II it is seen that V^{48}, Mn^{52}, Cu^{61}, Cu^{64} and Zn^{63} decay partly by K-capture; the energy of their K radiation is lower than 9 KV. The energy thus available, moreover, is negligible compared to that from their beta or positron emission. For instance, in the case of Mn^{52}, having a relatively low value of $\bar{E}_\beta = 85$ kev, the ionization energy available by electron capture is, at most, the product of the energy of the hardest K line (5.4 kv) times the fraction (0.65) of atoms decaying by electron capture, namely 3.5 kv; this is only 4.2 per cent of the ionizing energy of the positrons. For the other isotopes mentioned above this ratio is still lower. For this reason, the contribution of the energy released following electron capture is totally disregarded for those five elements in both Tables I and II.

Four other elements, Mn^{54}, Fe^{55}, Co^{58} and Zn^{65} likewise emit soft fluorescent radiation which can be considered like beta rays. In this group of elements, however, the contribution of the extra-nuclear radiation to tissue dosage cannot be neglected because the average energy per disintegration of the nuclear corpuscular radiation is either zero (Mn^{54}, Fe^{55}) or very small. In Table I, Group C, therefore, $\bar{E}_\beta$ and K_β take into account the fluorescent emission resulting from the disintegration of these elements by electron capture.

Obviously if the soft fluorescent radiation is treated like beta ray emission, its contribution to K_γ is neglected (Table II, Group B); however, its contribution to I_γ (corresponding to a fluorescent yield of $\omega_K \sim 0.3$) is stated in square brackets, only because similarly soft radiation can be measured in roentgens (23) and might be useful in standardization problems.

The two isotopes Y^{86} and In^{111} decay wholly by electron capture followed by gamma rays. Their K-radiation energies are 14.2 and 23.1 kev respectively; hence they cannot properly be considered absorbed in the same manner as beta rays. To absorb 95 per cent of them would require about 2 and 8 cm of tissue respectively, which is far greater than the ordinary beta ray range. Since these isotopes emit no beta rays, the contribution of electron-capture process to radiation dose is likely to be important for small organs. Accordingly I_γ and K_γ have been calculated by taking into account (for the sake of a first approximation) the K fluorescent yield $\omega_K = 0.65$ and 0.75 respectively (2). These values, enclosed by square brackets, are presented in Table II, Group B in addition to the I_γ and K_γ resulting from their gamma ray spectra.

The remaining fraction of the energy $(1-\omega_K)$ would be available in L radiation and Auger electrons. Since both are of extremely small penetrating power they have been placed under $\bar{E}_\beta$ and K_β (Table I, Group D), though no beta ray spectrum is present.

It is clear that the calculation of the total tissue dose, even for stable distributions, is in general a complex function of the type of radiation available and the dimensions of the tissue mass. As an illustration, curves are presented in Fig. 7 which show the variation of dose at the center of a sphere as a function of its radius. The curves are calculated for a uniform concentration of 1 μc/cc of In^{111} and illustrate the contribution to the dose by the different types of radiation emitted by this radioelement.

II-D. *Metabolic elimination.* Elimination of a radioisotope from a given tissue obviously affects the dose delivered since a fraction of the atoms initially present will not disintegrate there. It will be convenient, in the general case in which elimination is irregular, to plot the actual concentration (as affected by both elimination and decay)

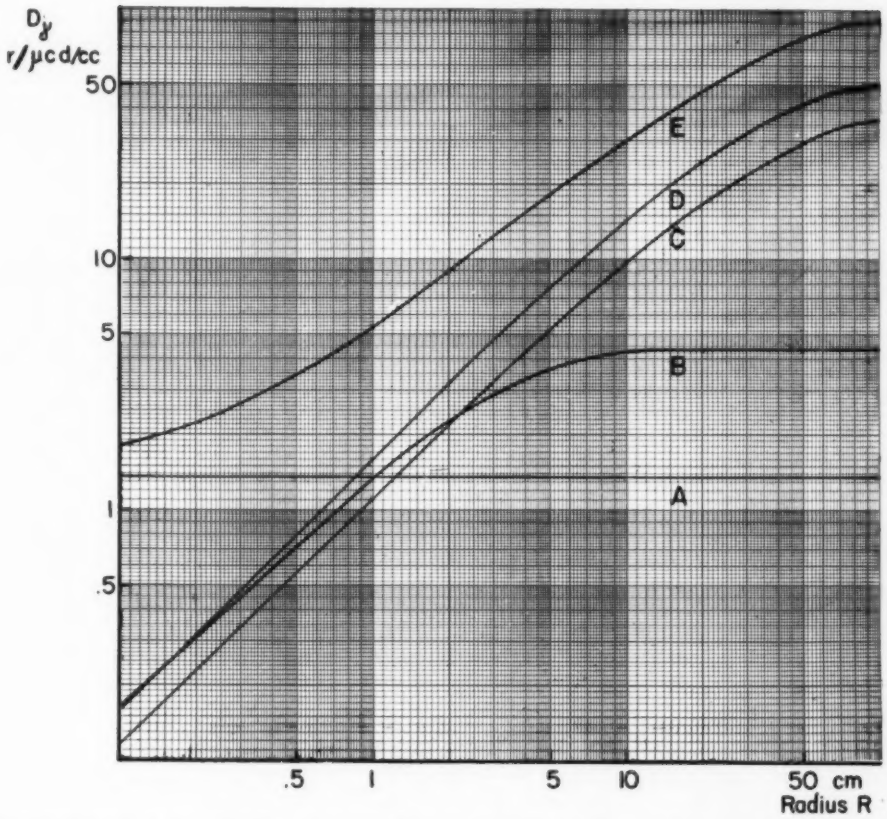

FIG. 7. Contribution of the gamma and x-radiation of In^{111} to the total tissue dose in roentgens at the center of a sphere as a function of the radius R of the sphere for a uniform concentration of one μc per cc completely disintegrated therein.

A: Auger electrons and L-radiation
B: K-radiation
C: 0.173 Mev gamma radiation
D: 0.247 Mev gamma radiation
E: Total tissue dose equals the sum of $A+B+C+D$

$C(t)\ e^{-\lambda t}$ as a function of time. (λ is the physical decay constant of the isotope.) The real beta ray dose Δ_β will be in general

$$\Delta_\beta = K_\beta \lambda \int_0^\infty C(t) e^{-\lambda t} dt \qquad \text{XIX}$$

since $K_\beta\lambda$ represents the dose per unit time. K_β and $C(t)$ retain the values chosen for equation I.

Similarly for a gamma ray emitter

$$\Delta_\gamma = K_\gamma \lambda \int_0^\infty g C(t) e^{-\lambda t} dt$$

with the proviso that calculation be extended to the whole organism. For the simple case of uptake times small compared to the half life of the isotope and in which $C(t)$ can be represented by the function $C_0\ e^{-\lambda_b t}$ (λ_b being the constant rate of elimination)

$$\Delta_\beta = C_0 K_\beta \lambda \int_0^\infty e^{-(\lambda_b+\lambda)t} dt = K_\beta C_0 \frac{\lambda}{\lambda+\lambda_b}$$

$$= D_\beta \frac{T_b}{T+T_b}$$

where the physical and biological half lives are

$$T = 0.693/\lambda \quad \text{and} \quad T_b = 0.693/\lambda_b.$$

Similarly

$$\Delta_\gamma = D_\gamma \frac{\lambda}{\lambda+\lambda_b} = D_\gamma \frac{T_b}{T+T_b}.$$

Hence in the case of *constant* rate of elimination in so far as total dose is concerned, the fundamental formulae I and III still apply, provided that by the half life is meant the *effective half life*

$$\frac{T \times T_b}{T + T_b}$$

of the isotope in the tissue as affected by both disintegration and elimination. This effective half life is the factor obtained directly from repeated measurements *in vivo* (Fig. 2).

II-E. *Miscellaneous formulae.* The *weight of one millicurie* of carrier free isotope can be readily calculated by noting that the weight of an atom of an element of atomic weight A is $(A/N)\times 10^3$ milligrams where $N = 6.02 \times 10^{23}$, Avogadro's number. Since one millicurie of an isotope contains $1.44 \times T \times 3.7 \times 10^7 \times 8.64 \times 10^4$ atoms (T in days) it follows that weight of one mc

$$1\text{ mc} = \frac{1.44 \times 3.7 \times 10^7 \times 8.64 \times 10^4 \times 10^3}{6.02 \times 10^{23}} \times A \times T$$

$$= 7.65 \times 10^{-9} \times T \times A \text{ milligram.} \qquad \text{XX}$$

Values derived from this formula for the various isotopes are presented in Table 1, column 10.

It seems of interest to close this paper with an illustration of the weights of radioelements necessary to produce marked radiation effects. This can be done by the following considerations. In order to deliver one e.r. to a tissue by means of a beta ray emitting isotope a concentration C is required such that

$$C = \frac{1}{88 \overline{E}_\beta T} \mu\text{c per gram of tissue.}$$

In terms of weight

$$C = \frac{7.66 \times 10^{-12} \times 10^{-3} \times A \times T}{88 \overline{E}_\beta T}$$

$$= 8.7 \times 10^{-17} \frac{A}{\overline{E}_\beta} \text{ gram per gram of tissue.}$$

As an example, for P^{32}, $A = 32$; $\overline{E}_\beta = 0.7$ Mev; hence for a lethal whole body dose of 1,000 r the concentration required is

$$C = \frac{8.7 \times 10^{-17} \times 32 \times 10^3}{0.7}$$

$$= 3.98 \times 10^{-12} \text{ gram per gram of body weight}$$

(a total of 0.28 μgram for a 70 kg man). Since phosphorus constitutes only 1.14×10^{-2} of the weight of the human body (1) only one atom in 2.85×10^9 atoms of phosphorus need be replaced on the average to obtain such an effect, on the assumption that no elimination takes place.

SUMMARY

When radioactive isotopes are employed either as tracers or in therapy, it is important to be able to determine the radiation dosage. This cannot, in general, be measured, but when the half life, radiation energy, and biological uptake and excretion are known, it can be calculated.

The paper is divided into two parts, based on clinical and physical aspects of the problem. In the physical part (Part II) are given mathematical developments of formulae for dosage rates and total doses for beta and gamma ray emitting isotopes, together with subsidiary formulae for safe concentration, weight per mc, etc. In the clinical part (Part I) these formulae are accepted, and doses considered for specific cases, for a number of isotopes of common interest. Particular consideration is given to the determination of safe tracer doses.

Since the basic information regarding radiation disintegration schemes and energies is scattered through many journals, it has been considered desirable to collect pertinent data. Two extensive tables are presented, for beta and gamma rays respectively, giving half life, radiation average energy, fraction disintegrating per day, and specific dosage data, including the safe tracer concentration, for some 38 isotope elements.

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DISCUSSION

DR. G. FAILLA, New York, N. Y. This is a very good and a very timely paper, especially as regards the doses which are permissible or which do not result in excessive irradiation of the body when the isotope is used for diagnostic purposes. As time goes on and isotopes and radiation of all kinds are used more and more, the question of protection becomes more important. As a matter of fact, at the present time there is quite a good deal of agitation to reduce the so-called tolerance dose or permissible daily dose of 1/10 r per day to a lower value, because a much larger proportion of the population is going to be exposed to radiation in the future and, if we consider genetic effects, particularly, the situation becomes quite serious.

But I think when it comes to diagnostic procedure, the doctor can always justify the administration of a certain amount of radiation because it is essential to make a proper diagnosis. On the other hand, he would not know how much radiation the body is getting, or a particular organ of the body is getting, without the information provided by this paper. It is not complete in the sense that, as usual, the physical side of the problem is much easier to solve than the biological side. Dr. Quimby has shown us how one can calculate the amount of radiation that is delivered to a particular organ or to the whole body when a certain amount of radioactive isotope is ingested or introduced into the body, but the difficulty is in knowing exactly how much of that is going to be concentrated in a particular organ, how long it is going to stay there, and so on, and also the relative sensitivity of that organ with respect to the whole body. Those are things that have to be obtained by biological experiments and clinical observations, and the time will come, of course, when we will know a great deal more about that.

At any rate, irrespective of all the biological factors, one must know first of all the amount that is present in a tissue; that is, one must know how much radiation a certain amount of radioactive isotope will give in a tissue, and that information has been provided now and one can determine the safe limit of the amount of radioactive isotope that can be used and not exceed, say, 1/10 r per day, or whatever figure the radiologist chooses to adopt.

As I said before, for diagnostic purposes it is justifiable to exceed that dose. For experimental purposes, in order to get information from the use of radioactive isotopes on patients, it is another matter. One should be very careful there because of legal complications, and also because one could do some harm.

I think when the paper is published, it will be very useful to a great many people, both radiologists and others who are now using radioactive isotopes for diagnosis of treatment.

DR. KENNETH E. CORRIGAN, Detroit, Mich. As usual, Dr. Quimby has presented a very excellent paper, a very timely one, a very necessary one, and one that is very well done indeed.

The biggest difficulty with all of this work at the present time, which she barely mentioned, is the fact that those things which are known are badly scattered. Due to the necessity of secrecy for a while, and to other perfectly natural causes, the information which would normally be collected in a few readily available journals is spread through many journals and through many reports that are just now being declassified, so that to do research in this field of the type that we want here is extremely difficult.

I am glad that the matter of the tolerance dose was mentioned. Our present concept of the tolerance dose is probably somewhat in error. Biological experimentation indicates that this may be true, and the tolerance dose for roentgen rays and gamma rays may very well be reduced. At the same time, there is evidence that the tolerance dose, as we now consider it, is not truly applicable to energetic particles, and the tolerance dose for beta rays may in the near future be something different from what we are now using.

This work is a solid foundation on which future studies of this sort may be built.

OPTICAL SYSTEMS FOR PHOTOFLUOROGRAPHY

PAPER II*

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CAMERAS that are to be used for recording the images of the fluorescent screen in photofluorography must have high speed and cover wide fields, but fortunately the demands that those requirements impose on the optical designer are encountered also in other fields. We owe to the requirements of one of the oldest sciences, astronomy, developments which are almost directly applicable to photofluorography; and since these developments came about in an attempt to correct the defects of ordinary astronomical telescopes, a summary of the simple theory of those defects probably will be of interest to radiologists.

An optical instrument designed to form images must gather a sufficient quantity of light and form a well-focused and sharp image of the object. The light-gathering power depends on the ratio of the focal length to the aperture; the smaller this ratio, the greater being the light-gathering power. When we say that a lens has a speed of f/2.0 we mean that the diameter of the usable aperture is one-half the focal length. The aperture is not always that of the lens itself, but may be a circular stop, real or virtual, which acts as the limit to the cone of rays taken in by the lens.

Light-gathering power is limited also by secondary factors, such as absorption of light by the glass, reflection from the surfaces of the lenses, and in the case of reflecting telescopes the efficiency of the metallic reflecting surface. The lens designer has techniques for reducing these secondary limiting factors but as he strives for greater and greater speed his primary effort is to develop systems with larger apertures and smaller focal length. As the f/number is increased, however, the difficulty of bringing the rays to a sharp focus increases at a higher and faster growing rate because of difficulties which are known as optical aberrations. These aberrations can be classified into various types and fall into two groups: (1) primary aberrations, which are described below and which can be controlled to a considerable extent by the optical designer; and (2) complex, or higher order, aberrations, which largely set the limit, in f/number and field, in acceptable performance. These latter aberrations depend primarily on the general type of optical system used and, in effect, the history of optical progress is largely the invention of new types which reduce these complex aberrations to a minimum. The descriptions of the primary aberrations follow. The higher order aberrations are similar in general character but because they are considerably more complex in detail they are not here described.

Chromatic Aberration. Chromatic aberration is the failure of an uncorrected lens to bring light of different colors to the same focus. All transparent substances transmit light with a speed which depends on the color or, more precisely, the wavelength. As a consequence, rays of different colors are bent through different angles upon entering or leaving the glass, and do not arrive at the same focal point. If we select as that point the common meeting place of, say, the rays of a particular wavelength in the green, then with an uncorrected lens there will be a halo of other

* For Paper I of the Series, see AM. J. ROENTGENOL. & RAD. THERAPY, January, 1948, *59*, 122–131

colors, noticeably blue and red, about each image point. The defect cannot be eliminated, but by the use of two or more lenses of different types of glass it can be reduced to a desired degree. Chromatic aberration is absent from reflectors coated metallically on the front surface since the angle of reflection for all colors is the same.

Geometrical Aberration. Even when the light is monochromatic no optical system will produce an image which is point for point and line for line a geometrically correct representation of the object because of the existence of faults that are known as "geometrical aberrations." These are five in number, namely:

(1) Spherical aberration
(2) Coma
(3) Astigmatism
(4) Curvature of field
(5) Distortion

In the first three of these aberrations there is failure to bring rays from a given object point to a common image point whereas in the last two the fault is a failure to produce in the image the same distribution of points in space as obtains in the object. In simple lens systems the geometric aberrations are apt to be severe, but even with skillful and complex optical design they can merely be reduced, never completely eliminated. The dependence of optical aberrations upon the aperture of the system and the angular size of image is shown in Table 1. The meaning of the two astigmatic defects will be discussed later. All except chromatic aberration are defects of reflectors as well as lenses.

For clarity in presentation the following paragraphs and illustrations deal with each aberration separately though actually, of course, all of them occur together in varying degrees whenever photographic images are formed. Most of the illustrations are from astronomy and the parallel light rays should be thought of as originating in a distant star lying sometimes on the axis of the lens and sometimes "off axis." If the optical system were perfect the image of the star would be a single sharply defined point.

Spherical Aberration. Spherical aberration is a fault caused by the spherical shape of lens or reflector surfaces. One cannot correct it for all object positions by changing the shape of the surfaces. A particular change of shape will correct the aberration only for a given object distance and position, and as a result of such a change the other four aberrations may even be affected adversely (Fig. 1).

Table 1

Aberration	Variation with Image Size I	Variation with Aperture A
Confusion disk due to spherical aberration	Independent	A^3
Confusion disk due to coma	I	A^2
Length of astigmatic lines	I^2	A
Astigmatic focal separation	I^2	Independent
Confusion disk due to curvature of field if film is flat	I^2	A
Distortion	I^3	Independent
Confusion disk due to longitudinal chromatic aberration	Independent	A
Confusion disk due to lateral chromatic aberration	I	Independent

The parallel light rays from a distant star lying on the axis of the system do not meet at the same image point, those passing through the center of the lens being focused

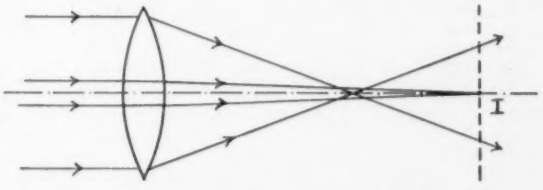

Fig. 1. Under-corrected spherical aberration.

at I, those passing through the outer zones of the lens being focused either nearer to or farther from the lens depending on whether the aberration is "under-corrected" or "over-corrected."

Coma. Contrasted with spherical aberration, coma is one of the defects found in images of stars *not* on the axis of the lens. In Figure 2 is illustrated a lens drawn so as

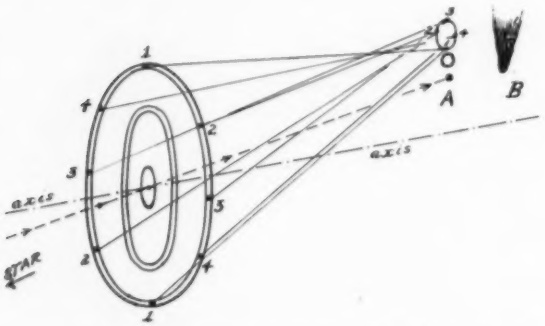

FIG. 2. Coma. *A* shows two comatic circles and point formed by light passing through three zones of the lens. *B* shows resulting comatic image from entire lens.

to show rays refracted through three zones, one at the edge, one somewhat nearer the middle, and one at the middle. For clarity the rays approaching the lens from the left are omitted. If coma and no other aberration is present, rays *1*, *1*, at top and bottom of the outer zone will meet at a common point (*1*) in the image picture (*A*). Rays *3*, *3*, will meet at point (*3*), and so on. Thus all the rays through this outermost zone of the lens will similarly meet in paired fashion to form a circle of light. Each such zone of the lens will form a similar circle of light, but the nearer to the middle of the lens, the smaller and brighter the circle will be. The light through the middle of the lens will form a bright point image, which will be nearest the axis, as shown in the figure, or, if the coma be opposite in effect, farthest away.

In (*B*), Figure 2 is represented the image of all the light of the star which passes through the lens, with a brush- or hair-like flare, called comatic flare, in the faintest part. This appearance gave rise to the name Coma, from the Greek for hair. Coma appears in many simple or complex forms depending on the system used, and only a simple type is illustrated here.

Astigmatism. This, too, is an off-axis aberration. As shown in Figure 3, the image of a point, such as a star off the axis, is not a point. Even if coma were reduced or eliminated, astigmatism would still result in a pair of lines, one closer to the lens than the other, and perpendicular to each other. Of course, in most cases both astigmatism and coma are present, and may be difficult to separate although characteristics of both may be seen. It is customary to talk of two astigmatic aberrations: length of astigmatic lines, which is dependent on the aperture of the lens, and astigmatic focal separation, which is not.

Curvature of Field. For each off-axis point in the object there will be a pair of astigmatic lines lying on curved surfaces represented by the dotted curves in Figure 4*A*. Even if the astigmatism is made negligible, there is still the problem of getting a plane image. If it is important to get rid of this curvature, usually an attempt is made to get the astigmatic focal curves

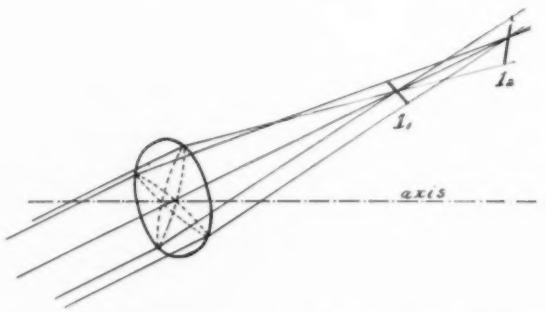

FIG. 3. Astigmatism causes a single point object to produce two line images.

to merge as nearly as possible over a large area of the image, as illustrated in Figure 4*B*.

Distortion. This is a failure to obtain uniform magnification over the entire field of view. Using a lens free from distortion the image of a grid of squares (Fig. 5*A*) will be like the object itself, with the same

magnification in all parts. When distortion is present, the image may appear barrel-shaped as in Figure 5*B* or pincushion-shaped as in Figure 5*C*.

Correction of Aberrations in Refractors. Since the aberrations are interdependent, the optical designer must balance corrections so as to obtain the best image for a given set of conditions. He has at his disposal the curvatures of lens surfaces, their separations, the different types of optical glass, and the placing of stops at strategic positions. Spherical surfaces are used, since techniques of lens making have not yet progressed to the point where surfaces other than spherical may be made easily and in quantity. The design of a highly corrected lens, to cover a large field, requires that enough elements of selected types of glass be assembled, the number sometimes going as high as six or seven. The surface reflections and glass absorption may easily become serious, although there are now methods for reducing the former by using so-called "coated lenses." If the aperture is large, however, as in the case of a celestial telescope, it may be quite difficult to make clear disks of glass of optical quality that are of large enough diameter.

Astronomical Reflectors. These difficulties led telescope makers to turn to reflectors, especially since earlier astronomical observations were mainly by eye and limited to a small field on the axis of the instrument. With a parabolic reflector a star image on the axis may be obtained which is free from chromatic and spherical aberration, and if other parts of the sky are to be observed visually, the astronomer may easily turn to them.

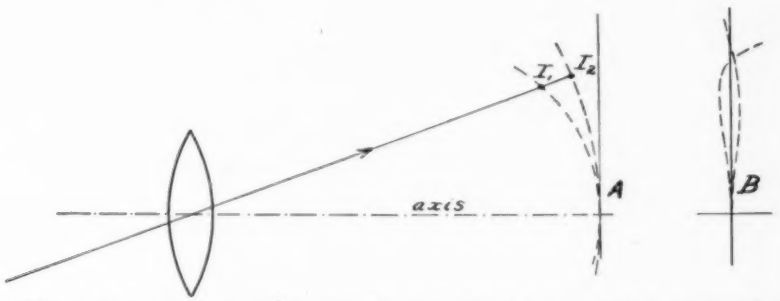

Fig. 4. Curvature of field. *A*, dotted lines show two astigmatic focal curves. *B*, some correction has been made.

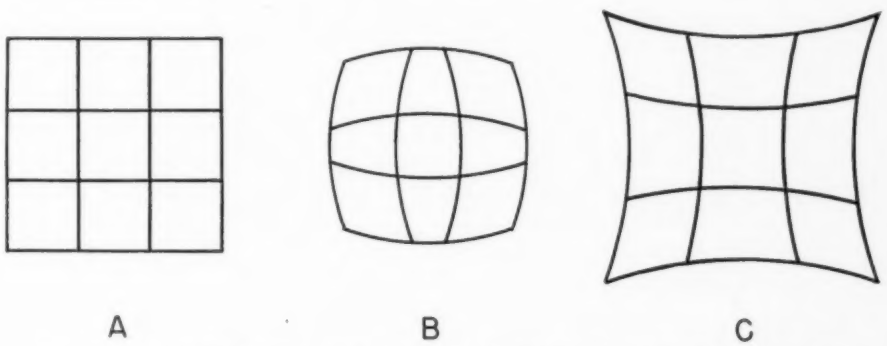

Fig. 5. *A*, no distortion; *B*, barrel-shaped distortion; *C*, pincushion distortion.

Diffraction. Because of its wave nature, light gathered by a lens or mirror invariably is focused as a disk rather than a true point even though the source of the light be a point. In most astronomical work point images are greatly desired and camera designers exert much effort to reduce to a minimum the diameter of the image disk,

which is known as the circle of confusion. All else being equal, the smaller the f/number of the optical system, the smaller will be the circle of confusion, but, of course, there is no advantage in reducing disk diameter below the resolving power of the photographic material that is being used to record the stellar images.

The Schmidt Telescope. Photography, bringing with it the demand for still larger apertures and high quality over larger field areas, stimulated the search for large aperture reflecting systems which would be free from the oblique aberrations, principally coma and astigmatism. In scientific research the celestial telescope is really a giant camera, and it is becoming customary to call it one. The problems of the camera lens designer are also those of the telescope maker. Used photographically, the telescope takes on the characteristics of a camera lens, requiring good image quality over a large field. At first, combinations of mirrors were used, the most notable contribution being that of Schwarzschild in 1905. He designed a reflecting system of two mirrors, free from coma and spherical aberration, having a flat field, and with the astigmatism balanced on two sides of the image plane. But while his research constitutes a high point in the theoretical study of aberrations, this did not solve the problem, for the speed of his design is no greater than f/3. Also, its overall length is too great for practical use.

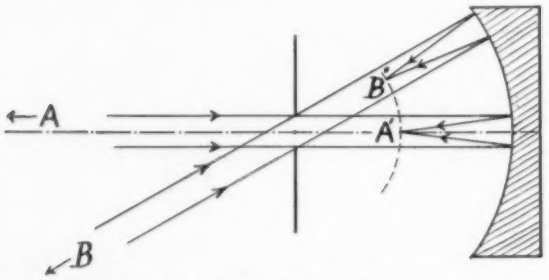

Fig. 6. Spherical mirror with small aperture at center of curvature. Such a system yields equally good images for all parts of the field but its speed is low.

The difficulty was finally overcome in a novel manner, in 1931, by a telescope maker named Bernhard Schmidt, employed at the Hamburg Observatory in Bergedorf, Germany. The development of Schmidt's revolutionary idea will be first illustrated by reference to Figure 6.

An opaque diaphragm with a small aperture is placed at the center of curvature of a spherical mirror. Parallel rays from a distant point, A, on the axis will meet at a focus A', midway between the diaphragm and the vertex of the mirror. If the aperture is small there will be negligible aberration since only a small part of the mirror is used for these rays.

Since the mirror is spherical, point B also is on the axis and the narrow bundle of rays orginating at B is focused at B'. The same will be true for all other object positions and the resulting image surface is represented by a curved dotted line.

The drawback in the design represented in Figure 6 is the restricted aperture. But suppose we open it and put in a corrector plate P, Figure 7, with one surface so shaped that all of the rays through the enlarged opening are reflected to a common point. Then we have a corrected reflecting telescope of a sort never before conceived. Truly it is difficult to figure such a corrector plate, but Schmidt found that he could correct the coma and spherical aberration over a much larger area than by any other means.

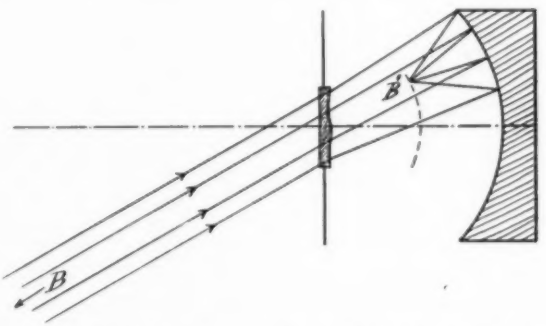

Fig. 7. Schmidt camera. An aspherical correcting plate at the center of curvature redirects the rays so that they are reflected to a good image point.

The chromatic aberration of the correc-

tor plate is negligible and if it is made of quartz the telescope can be used to photograph wavelengths in the ultraviolet. This is a tremendous advantage over the refracting telescope, since transparent materials which will transmit the ultraviolet are limited in variety and unavailable in large sizes.

The field is spherical rather than flat but this drawback can usually be overcome in a surprising number of cases by bending or warping the film, and in some Schmidt cameras of relatively long focal length it can be overcome by adding a correcting lens placed very close to the film plane. In such a position the lens, usually plane on the side nearest the film, has very little effect on the focal length of the system, but flattens the image plane effectively. For large fields and at short focal lengths a corrector cannot be used with success.

At one stroke, Schmidt overcame two difficulties in celestial photography—restriction to small fields and limited relative apertures—and led the way in overcoming them in all other applications of optics.

Other Applications of the Schmidt Principle. After Schmidt had shown how his camera could be built the theory was quickly developed. This naturally opened the way to new possibilities in the design of similar systems, all using combinations of mirrors and thin refracting plates. This sort of combination of reflecting and refracting surfaces is known as a *catadioptric system.* In a variety of forms it has been adapted to astronomy, spectroscopy, television, and many other uses, now including photofluorography.

A drawback to the manufacture of the Schmidt camera is the great skill required to figure the aspherical corrector plate. Other catadioptric systems are easier to make. One of the earliest is a reflector invented over fifty years ago by Alphonse Mangin for projection of a beam of light. The reflector has the shape of a negative meniscus metallically coated for high reflection on the rear instead of the front face, and by choosing the radii suitably the spherical aberration can be corrected. In a sense, Mangin's invention is a forerunner of catadioptric systems for image formation.

About ten years after Schmidt developed his camera, Maksutov in Russia patented a spherical reflector combined with a corrector plate which was a thin meniscus with spherical surfaces. He has since developed many variants of this design (Fig. 8),

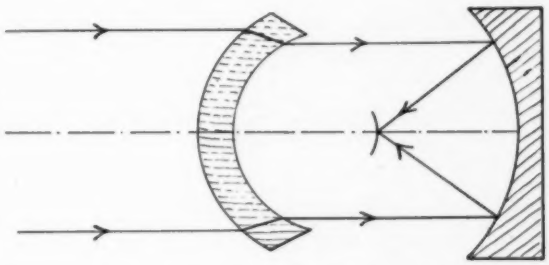

FIG. 8. Maksutov camera. A catadioptric system in which the correcting element is not a Schmidt plate but instead a meniscus with spherical surfaces.

which is highly successful for celestial telescopes. With a given thickness and with the proper choice of radius the chromatic aberration of the meniscus is zero and the residual spherical aberration quite small. By proper adjustment of the location of the surfaces the coma can be reduced.

There is an analogy between the catadioptric system and the corrected lens of the older type. When a lens is corrected by combining two lens elements, a negative and a positive, the spherical aberration of one is compensated by the opposite spherical aberration of the other; similarly, in a catadioptric system, the spherical aberrations of the meniscus and the reflector are opposite in sign. They are not quite equal, however, so that there remains a slight residual aberration, tolerable for focal ratios slower than F/1.5 or thereabouts, if the field of view is also rather small. Maksutov suggests reducing this residual aberration in some cases by modifying the sphericity of the surfaces to a very slight degree.

About the same time that Maksutov was developing his meniscus type instruments, others were developing modifications of the Schmidt type camera. These are too numerous to mention here, and the reader is referred to the bibliography for information regarding them. For ultra high speed cameras having large field, with moderate sized elements, a highly successful system is that used in the family of cameras developed recently by Henyey and Greenstein. Here the meniscus is made of two elements, the combination having external surfaces which are concentric. The glasses used have the same index of refraction and different dispersions. The centers of curvature of the external surfaces of the meniscus and of the reflector and the plateholder are all the same. This means that over the whole field the system can be considered to have the characteristics of an axial system, making possible correction of the off-axis aberrations to a high degree. This system is particularly valuable in photofluorography, where high speed and large angle are absolutely essential.

The attached bibliography is not expected to be a complete reference list to reading material on catadioptric systems. Many important developments are probably not available now because the requirements of national security still prevent their publication. The first group of papers should be easy reading for the layman. Those in the second group are mathematical and technical in the presentation.

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EDITORIALS

A CONGENITAL SYNDROME OF MECHANICAL ORIGIN

A NUMBER of cases of prenatal bowing and angulation of a single tubular bone or of a pair of tubular bones have been reported. Among the commonest of these deformities is congenital anterior curvature of one or both tibias or congenital tibial kyphosis. Chapple and Davidson have described a case of a newborn infant who presented congenital symmetrical lateral bowing of the femurs with bilateral dislocation of the hips, while the remainder of the skeleton apparently was normal, and the "position of comfort" assumed by the infant did not suggest faulty fetal position of the arms. Another observer has reported associated bendings in the femoral shafts of a newborn infant, who also exhibited bilateral tibial kyphosis and talipes equinus. It is of interest to note, however, that there were no concomitant deformities of the bones in the upper extremities in these cases reported which exhibited congenital curved deformities in the bones of the lower extremities.

Quite recently, Caffey[1] has reported prenatal bowing and thickening of tubular bones, with multiple cutaneous dimples in arms and legs. Included in Caffey's report are three cases of infants each of whom had congenital symmetrical bowings of the femoral and humeral shafts and similar, but sometimes unpaired, deformities of the shafts of the tibias, radiuses and ulnas. In each case the bowed diaphyseal segments were thickened, as well as bent. All curvatures extended through substantial longitudinal segments of the shafts in or near their middle thirds and large symmetrical cutaneous dimples overlay the salient angles of the curves in several of the deformed bones.

Caffey comments that certain positive findings were common in all his cases. Multiple bowing deformities of the tubular bones of the extremities were present at birth, and the nature and magnitude of the skeletal lesions suggested that they had been developing a long time prior to birth. Each case was characterized by symmetrical lateral bowings of the femurs and symmetrical posterior bowings of the humeri. However, distal to the knees and the elbows the deformities of the bones were usually not symmetrical. At birth the cortical segments on the concave sides of the bony curves were thickened inwardly while the corresponding cortical segments on the convex sides of the same curves were unusually thin. Multiple cutaneous dimples were present in the deformed extremities in two of his cases.

The infants were born of healthy mothers and there was no evidence of inherited or familial skeletal or cutaneous disease. The infants themselves were healthy except for the deformities and the disabilities due to the deformities. The skeletal lesions were confined to the long tubular bones of the limbs; the bones of the hands, feet, head, thorax, pelvis and spine were not affected. Neither were there morbid changes demonstrated save in the skeleton and in the skin. There was no evidence of any of the intrinsic prenatal skeletal dysplasias which bring about deformities of the long bones of the fetus such as achondroplasia or dyschondroplasia. Neither was there evidence of osteogenesis imperfecta or pseudarthrosis. There was no clinical, roentgenographic, or serological evidence of prenatal or infantile rickets or syphilis.

[1] Caffey, John. Prenatal bowing and thickening of tubular bones, with multiple cutaneous dimples in arms and legs; a congenital syndrome of mechanical origin. *Am. J. Dis. Child.*, 1947, *74*, 543–562.

While the pathogenesis of these prenatal deformities cannot be established by direct observation, Caffey brings forth considerable convincing evidence in support of the hypothesis that the bony lesions resulted solely from mechanical disturbances in utero, secondary to elocation of the fetal arms and legs. He speculates that these skeletal deformities may be explained satisfactorily by assuming that the fetal arms and legs were packed in attitudes which permitted the transmission of deforming uterine pressures from one impacted fetal part to another, and that the cutaneous dimplings, in like fashion, were brought about by pressure over the uterine wall on the fetal skin compressed on ectopic exposed bony points of the fetus.

Multiple angulations of the shafts due to prenatal fractures secondary to pseudarthrosis Caffey could easily exclude as the cause of the deformities of the bones in his cases as none of the cardinal signs of pseudarthrosis, such as focal degeneration of the bones, pathological fractures or false motion at the site of the diaphyseal angulation was evident in any of his cases.

From the analysis of his patients, Caffey concluded that the cutaneous dimples, the bowing of the long bones and the cortical thickening in the curved segments of the bones are all consonant with the hypothesis of simple mechanical molding of the displaced fetal arms and legs. He accepts Browne's postulate that ectopic dimples are stigmas of fetal compression. These dimples develop in the fetal skin in the sites of points of pressure between the maternal uterine wall and the superficial, sharp bony prominences of the fetal skeleton. The cutaneous depressions represent localized pressure atrophy of the subcutaneous soft tissues caught between the overlying uterine wall and the underlying bony prominences of the fetus.

Caffey states that the bowings of the tubular bones present at birth could have been caused by mechanical bending forces to which these bones were subjected long before birth, probably at first during an early phase of fetal life, when these bones were largely cartilaginous and more easily bent. However, abnormal fetal position alone is insufficient to explain these skeletal deformities and Caffey postulates abnormal fetal posture in each case, one in which compressing forces were applied to the deformed bones at the sites of their concavities, and he calls attention to one feature of the bone lesions which was common to all three cases, namely the symmetrical lateral bowings of the femurs and the symmetrical dorsal bowings of the humeri. He states that the fetal extremities need only be folded into a cross leg and cross arm pattern, in which each foot presses on the internal aspect of its opposite thigh and each hand impinges on the flexor surface of its opposite upper arm, to bring about such deformities.

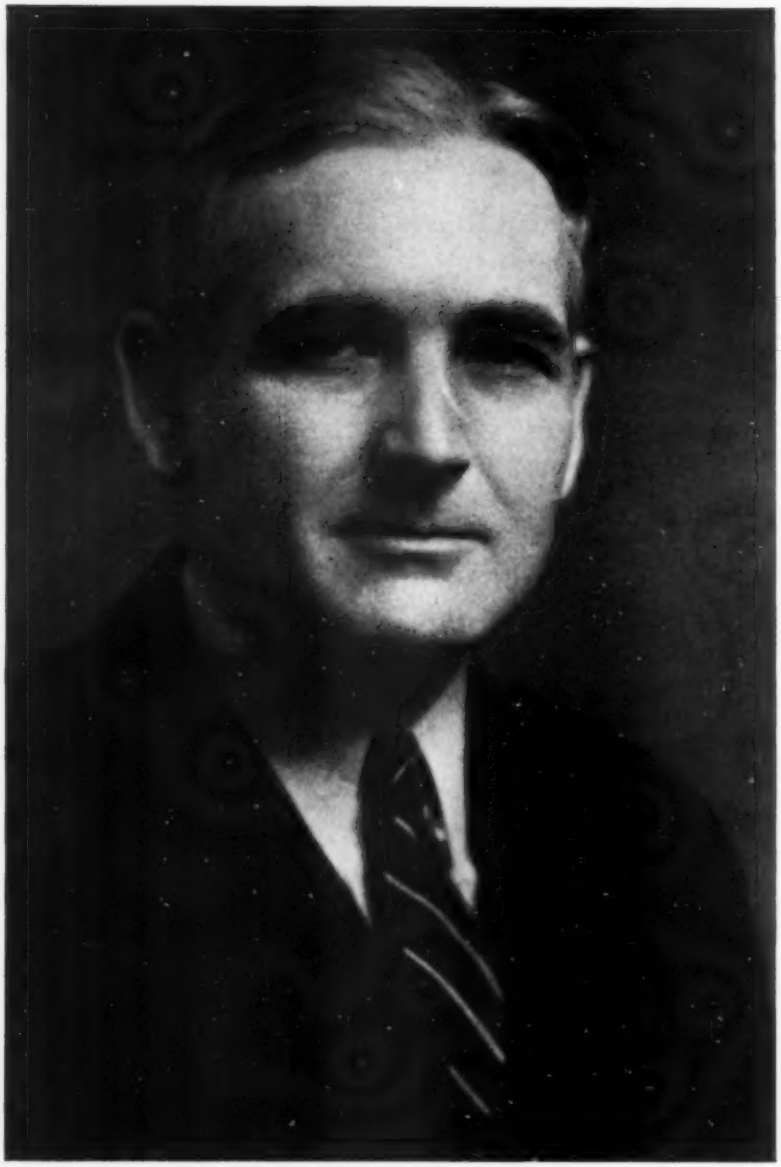
One of the striking features at birth of every one of the bowed bones is the thickening of the cortical segment on the concave wall of the curve and thinning of the opposite cortical segment on the convex wall of the curve. These cortical thickenings are limited to the curve itself, and all are directed inward; the caliber of the contiguous medullary cavity is correspondingly reduced. As a result of the analysis of the bone deformities in his cases, Caffey states that it is clear that this cortical hypertrophy represents accretion due to failure of absorption of the cortex from within and, on the other hand, does not represent subperiosteal accretion of the external cortical surface. This combination of cortical thickening on the concavity and cortical thinning on the convexity is, in Caffey's opinion, another example of structural adaptation of the affected bones to prenatal extraskeletal forces of compression which operated at the sites of the cortical thickenings.

The gradual postnatal regression of the bowings of the bones and of the cortical thickenings which Caffey noted in his cases further confirmed his opinion of the structural adaptation of the bone to disturbed fetal mechanics. He points out that the presence of bowed legs and crooked,

thickened bones with tibial and femoral spurring in his cases as late as two years after birth demonstrates that the late infantile clinical and roentgenographic changes residual to prenatal mechanical bowing closely resemble the deformities of healed early rickets and that this type of nonrachitic bowed legs might easily be mistaken for rachitic bowed legs, especially in the absence of cutaneous dimples or when the cutaneous dimples are present they are improperly interpreted, and he thinks it is quite probable that some of the cases that have been reported as instances of infantile tibial osteochondrosis were actually examples of prenatal bending of the bones in the legs, and he cautions against diagnosis of infantile tibial osteochondrosis unless necrosis of the medial tibial condyle is associated with bowing and medial spurring of tibias and femurs.

From Caffey's careful analysis of his group of cases he concludes that the cause and pathogenesis of the skeletal and cutaneous lesions have not been determined with certainty but there was much evidence in his cases which suggests that these deformities were caused by mechanical compression in utero operating on ectopic fetal extremities and that prenatal mechanical molding of the bones and pressure atrophy of the fetal skin are the probable pathogenetic mechanisms, and he emphasizes the similarity of this type of bowed legs caused by prenatal molding and the bowed legs due to rickets and to Blount's tibial osteochondrosis.

There is much in Caffey's discussion both from the clinical and the roentgenographic findings in his cases to warrant the deductions which he has made concerning prenatal bowing and thickening of the tubular bones with multiple cutaneous dimples in arms and legs and he thinks this is definitely a congenital syndrome of mechanical origin.



HARRY L. FARMER

1896–1947

DR. HARRY L. FARMER died December 6, 1947, at his home in Shaker Heights, Cleveland, Ohio. The cause of death was coronary thrombosis. He had been ill for a few months with congestive heart failure in the spring of 1947, but had resumed almost full time work again at the time of his death.

Dr. Farmer was born in Comanche, Texas, in 1896, and graduated from Baylor University Medical School in 1918. He went into service in the United States Navy Medical Corps where he served a year, during and after World War I. His internship was served at the Cincinnati General Hospital. Under Dr. George W. Holmes at

Massachusetts General Hospital, he obtained his radiological training during the years 1921–1923. He came to Cleveland to head the Radiological Department at City Hospital in 1923 and later joined the partnership with Dr. Walter C. Hill, Dr. George Thomas, and Dr. Merthyn A. Thomas, with whom he continued to practice. Dr. Farmer joined the American Roentgen Ray Society in 1928. He became a diplomate of the American Board of Radiology in 1934.

Dr. Farmer's many friends and his professional confrères will remember with inspiration his absolute integrity and his warm friendliness. He exemplified perfectly the adage of an older generation "... there is always time for courtesy." His dependability and sense of duty kept him at work day after day, especially during the war years when fatigue and real physical anguish must have begged for relief. No pressure of work could force him to hasty or superficial judgment, and unselfish intellectual honesty pervaded his professional work throughout his entire life-time.

He will be missed by his associates and the entire radiological profession of Cleveland.

WALTER C. HILL

SOCIETY PROCEEDINGS, CORRESPONDENCE AND NEWS ITEMS

Items for this section solicited promptly after the events to which they refer

MEETINGS OF ROENTGEN SOCIETIES*

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AMERICAN ROENTGEN RAY SOCIETY
Secretary, Dr. H. Dabney Kerr, University Hospital, Iowa City, Iowa. Annual meeting: Palmer House, Chicago, Ill., Sept. 14–17, 1948.

AMERICAN RADIUM SOCIETY
Secretary, Dr. H. F. Hare, 605 Commonwealth Ave., Boston, Mass. Annual meeting: Stevens Hotel, Chicago, Ill., June 20–22, 1948.

RADIOLOGICAL SOCIETY OF NORTH AMERICA
Secretary, Dr. D. S. Childs, 607 Medical Arts Bldg., Syracuse, N. Y. Annual meeting: 1948, to be announced.

AMERICAN COLLEGE OF RADIOLOGY
Secretary, Mac F. Cahal, 20 N. Wacker Drive, Chicago 6. Annual meeting: Continental Hotel, Chicago, Ill., June 20, 1948.

SECTION ON RADIOLOGY, AMERICAN MEDICAL ASSOCIATION
Secretary, Dr. U. V. Portmann, Cleveland Clinic, Cleveland, Ohio. Annual meeting: Chicago, Ill., June 21–25, 1948.

ALABAMA RADIOLOGICAL SOCIETY
Secretary, Dr. C. S. Stickley, 515 Bell Bldg., Montgomery, Ala. Next meeting time and place of Alabama State Medical Association.

ARKANSAS RADIOLOGICAL SOCIETY
Secretary, Dr. Fred Hames, 511 National Bldg., Pine Bluff, Ark. Meets every three months and also at time and place of State Medical Association.

BROOKLYN ROENTGEN RAY SOCIETY
Secretary, Dr. A. H. Levy, 1354 Carroll St., Brooklyn 13, N. Y. Meets monthly on fourth Tuesday, October to April.

BUFFALO RADIOLOGICAL SOCIETY
Secretary, Dr. Mario C. Gian, 610 Niagara St., Buffalo, N. Y. Meets second Monday evening each month, October to May inclusive.

CENTRAL NEW YORK ROENTGEN RAY SOCIETY
Secretary, Dr. Dwight V. Needham, 608 E. Genesee St., Syracuse, N. Y. Three meetings a year. January, May, November.

CHICAGO ROENTGEN SOCIETY
Secretary, Dr. T. J. Wachowski, 310 Ellis Ave., Wheaton, Ill. Meets second Thursday of each month October to April inclusive at the Palmer House.

CINCINNATI RADIOLOGICAL SOCIETY
Secretary, Dr. Eugene L. Saenger, 735 Doctors Bldg., Cincinnati 2, Ohio. Meets last Monday of each month, September to May, inclusive.

CLEVELAND RADIOLOGICAL SOCIETY
Secretary, Dr. George L. Sackett, 10515 Carnegie Ave. Cleveland 6, Ohio. Meetings at 6:30 P.M. on fourth Monday of each month from October to April.

DALLAS-FORT WORTH ROENTGEN STUDY CLUB
Secretary, Dr. X. R. Hyde, Medical Arts Bldg., Fort Worth, Texas. Meets in Dallas on odd months and in Fort Worth on even months, on third Monday, 7:30 P.M.

DENVER RADIOLOGICAL CLUB
Secretary, Dr. Mark S. Donovan, 306 Majestic Bldg., Denver 2, Colo. Meets third Friday of each month at Department of Radiology, Colorado School of Medicine.

DETROIT ROENTGEN RAY AND RADIUM SOCIETY
Secretary, Dr. E. R. Witwer, Harper Hospital. Meets monthly on first Thursday from October to May, at Wayne County Medical Society Building.

FLORIDA RADIOLOGICAL SOCIETY
Secretary, Dr. J. A. Beals, St. Luke's Hospital, Jacksonville, Fla. Meets twice yearly, in April preceding annual meeting of Florida Medical Society, and in November.

GEORGIA RADIOLOGICAL SOCIETY
Secretary, Dr. Robert Drane, DeRenne Apartments, Savannah, Ga. Meets in mid-winter and at annual meeting of Medical Association of Georgia in the spring.

RADIOLOGICAL SOCIETY OF KANSAS CITY
Secretary, Dr. Arthur B. Smith, 800 Argyle Bldg., Kansas City, Mo. Meets third Thursday of each month.

ILLINOIS RADIOLOGICAL SOCIETY
Secretary, Dr. Wm. DeHollander, St. John's Hospital, Springfield, Ill. Meets three times a year.

INDIANA ROENTGEN SOCIETY
Secretary, Dr. J. A. Campbell, Indiana University Hospitals, Indianapolis 7. Meets second Sunday in May.

IOWA X-RAY CLUB
Secretary, Dr. Arthur W. Erskine, 326 Higley Bldg., Cedar Rapids, Iowa. Luncheon and business meeting during annual session of Iowa State Medical Society. Special meetings by announcement.

KENTUCKY RADIOLOGICAL SOCIETY
Secretary, Dr. W. C. Martin, 321 W. Broadway, Louisville. Meets annually in Louisville on first Saturday in Apr.

LONG ISLAND RADIOLOGICAL SOCIETY
Secretary, Dr. Marcus Wiener, 1430-48th St., Brooklyn, N. Y. Meets Kings County Med. Soc. Bldg. monthly on fourth Thursday, October to May, 8:30 P.M.

LOS ANGELES RADIOLOGICAL SOCIETY
Secretary, Dr. Moris Horwitz, 441 No. Camden Drive, Beverly Hills, Calif. Meets second Wednesday each month at Los Angeles County Medical Assn. Building.

LOUISIANA RADIOLOGICAL SOCIETY
Secretary, Dr. J. R. Anderson, 1130 Louisiana Ave., Shreveport. Meets annually during Louisiana State Medical Society Meeting.

LOUISVILLE RADIOLOGICAL SOCIETY
Secretary, Dr. E. L. Pirkey, Louisville General Hospital, Louisville 2, Ky. Meets monthly on second Friday at Louisville General Hospital.

MICHIGAN ASSOCIATION OF ROENTGENOLOGISTS
Secretary, Dr. R. D. McDuff, 220 Genesee Bank Bldg., Flint 3, Mich.

MILWAUKEE ROENTGEN RAY SOCIETY
Secretary, Dr. C. A. H. Fortier, 231 W. Wisconsin Ave., Milwaukee, Wis. Meets monthly on second Monday at University Club.

MINNESOTA RADIOLOGICAL SOCIETY
Secretary, Dr. Chauncey N. Borman, 802 Medical Arts Bldg., Minneapolis 2, Minn. Two meetings yearly, one at time of Minnesota State Medical Association the other in the fall.

* Secretaries of societies not here listed are requested to send the necessary information to the Editor.

Nebraska Radiological Society
Secretary, Dr. Ralph C. Moore, Nebraska Methodist Hospital, Omaha 3, Nebr. Meets third Wednesday of each month, at 6 P.M. at either Omaha or Lincoln.

New England Roentgen Ray Society
Secretary, Dr. George Levene, Massachusetts Memorial Hospitals, Boston, Mass. Meets monthly on third Friday, Boston Medical Library.

New Hampshire Roentgen Ray Society
Secretary, Dr. A. C. Johnston, Elliott Community Hospital, Keene, N. H. Meets four to six times yearly.

New York Roentgen Society
Secretary, Dr. Ramsay Spillman, 115 East 61st St., New York City. Meets monthly on third Monday, New York Academy of Medicine, at 8:30 P.M.

North Carolina Radiological Society
Secretary, Dr. J. E. Hemphill, 323 Professional Bldg., Charlotte 2, N. C. Meets in May and October.

North Dakota Radiological Society
Secretary, Dr. C. O. Heilman, 807 Broadway, Fargo. Meetings held by announcement.

Ohio State Radiological Society
Secretary, Dr. Carroll C. Dundon, 2065 Adelbert Road, Cleveland 6, Ohio. Next meeting at annual meeting of Ohio State Medical Association, Cincinnati, Ohio, March 31, 1948.

Oklahoma State Radiological Society
Secretary, Dr. P. E. Russo, 230 Osler Bldg., Oklahoma City, Okla. Three regular meetings annually.

Oregon Radiological Society
Secretary, Dr. William Y. Burton, 242 Medical Arts Bldg., Portland 5, Oregon. Meets monthly 2nd Wednesday, 8:00 P.M., Library of University of Oregon Medical School.

Orleans Parish Radiological Society
Secretary, Dr. Joseph V. Schlosser, Charity Hospital, New Orleans 13, La. Meets first Tuesday of each month.

Pacific Northwest Radiological Society
Secretary, Dr. S. J. Hawley, 1320 Madison St., Seattle 4, Wash. Meets annually in May.

Pacific Roentgen Society
Secretary, Dr. L. H. Garland, 450 Sutter St., San Francisco, Calif. Meets annually, during meeting of California Medical Association.

Pennsylvania Radiological Society
Secretary, Dr. J. M. Converse, 416 Pine St., Williamsport. Annual meeting, May 21–22, 1948, Erie, Pa., at Hotel Lawrence.

Philadelphia Roentgen Ray Society
Secretary, Dr. C. L. Stewart, Jefferson Hospital. Meets, first Thursday of each month, October to May, at 8:00 P.M., in Thomson Hall, College of Physicians.

Pittsburgh Roentgen Society
Secretary, Dr. R. P. Meader, 4002 Jenkins Arcade Pittsburgh 22, Pa. Meets 6:30 P.M. at Webster Hall Hotel on second Wednesday each month, October to May inclusive.

Radiological Section, Baltimore Medical Society
Secretary, Dr. Harry A. Miller, 2452 Eutaw Place, Baltimore. Meets third Tuesday each month, September to May.

Radiological Section, Connecticut Medical Society
Secretary, Dr. Robert M. Lowman, Grace-New Haven Community Hospital, New Haven 11, Conn. Meets bimonthly on second Thursday, at place selected by Secretary.

Radiological Section, Southern Medical Association
Secretary, Dr. Roy G. Giles, Temple, Texas.

Radiological Society of New Jersey
Secretary, Dr. Raphael Pomeranz, 31 Lincoln Park, Newark, N. J. Meets annually at time and place of State Medical Society. Mid-year meetings at place chosen by president.

Rochester Roentgen Ray Society, Rochester, N. Y.
Secretary, Dr. Murray P. George, Strong Memorial Hospital. Meets monthly on third Monday from October to May, inclusive, 8 P.M. at Strong Memorial Hospital.

Rocky Mountain Radiological Society
Secretary, Dr. Maurice D. Frazer, 1037 Stuart Bldg., Lincoln, Nebr. Meets in Salt Lake City, Utah, 1948.

St. Louis Society of Radiologists
Secretary, Dr. Edwin C. Ernst, Beaumont Medical Building, St. Louis, Mo. Meets fourth Wednesday of each month, except June, July, August, and September.

San Diego Roentgen Society
Secretary, Dr. R. F. Niehaus, 1831 Fourth Ave., San Diego, Calif. Meets monthly, first Wednesday at dinner.

Section on Radiology, California Medical Association
Secretary, Dr. D. R. MacColl, 2007 Wilshire Blvd., Los Angeles 5, Calif.

Section On Radiology, Illinois State Medical Society
Secretary, Dr. H. W. Ackemann, 321 W. State St., Rockford, Ill.

Shreveport Radiological Club
Secretary, Dr. R. W. Cooper, Charity Hospital, Shreveport, La. Meets monthly on third Wednesday, at 7:30 P.M., September to May inclusive.

South Carolina X-Ray Society
Secretary, Dr. T. A. Pitts, Baptist Hospital, Columbia, S. C. Meets in Charleston on first Thursday in November, also at the time and place of South Carolina State Medical Association.

Tennessee Radiological Society
Secretary, Dr. J. M. Frère, 707 Walnut St., Chattanooga, Tenn. Meets annually at the time and place of the Tennessee State Medical Association.

Texas Radiological Society
Secretary, Dr. R. P. O'Bannon, 650 Fifth Ave., Fort Worth 4, Texas.

University of Michigan Department of Roentgenology Staff Meeting
Meets each Monday evening from September to June, at 7 P.M. at University Hospital.

University of Wisconsin Radiological Conference
Secretary, Dr. E. A. Pohle, 1300 University Ave., Madison, Wis. Meets first and third Thursdays 4:00 to 5:00 P.M., September to May inclusive. Room 203, Service Memorial Institute, 426 N. Charter St., Madison.

Utah Radiological Conference
Secretary, Dr. Henry H. Lerner, School of Medicine, University of Utah, Salt Lake City 1. Meets 1st and 3rd Thursdays monthly from 7:30 to 10 P.M., Salt Lake County General Hospital, September to June.

Utah State Radiological Society
Secretary, Dr. M. Lowry Allen, Judge Bldg., Salt Lake City 1, Utah. Meets third Wednesday in September, November, January, March and May.

Virginia Radiological Society
Secretary, Dr. P. B. Parsons, Norfolk General Hospital, Norfolk, Va. Meets annually in October.

Washington State Radiological Society
Secretary, Dr. Homer V. Hartzell, 310 Stimson Bldg., Seattle 1, Wash. Meets fourth Monday each month, October through May, College Club, Seattle.

X-RAY STUDY CLUB OF SAN FRANCISCO
Secretary, Dr. Ivan J. Miller, 2000 Van Ness Ave. Meets monthly on third Thursday at 7:45 P.M., first six months of year at Lane Hall, Stanford University Hospital, and second six months at Toland Hall, University of California Hospital.

CUBA

SOCIEDAD DE RADIOLOGÍA Y FISIOTERAPIA DE CUBA
President, Dr. J. Manuel Viamonte, Hospital Mercedes, Habana, Cuba. Meets monthly in Habana.

MEXICO

SOCIEDAD MEXICANA DE RADIOLOGIA Y FISIOTERAPIA
General Secretary, Dr. D. P. Cossio, Marsella No. 11, Mexico, D. F. Meets first Monday of each month.

BRITISH EMPIRE

BRITISH INSTITUTE OF RADIOLOGY INCORPORATED WITH THE ROENTGEN SOCIETY
Medical Members' meeting held monthly on third Friday at 2:30 P.M. and Ordinary Meeting at same time on following Saturday, October to May, 32 Welbeck St., London, W.1.

FACULTY OF RADIOLOGISTS
Secretary, Dr. M. H. Jupe, 23 Welbeck St., London, W.1 England.

SECTION OF RADIOLOGY OF THE ROYAL SOCIETY OF MEDICINE (CONFINED TO MEDICAL MEMBERS)
Meets third Friday each month at 4:45 P.M. at the Royal Society of Medicine, 1 Wimpole St., London.

CANADIAN ASSOCIATION OF RADIOLOGISTS
Honorary Secretary, Dr. E. M. Crawford, 2100 Marlowe Ave., Montreal 28, Que. Meetings January and June.

SECTION OF RADIOLOGY, CANADIAN MEDICAL ASSOCIATION
Secretary, Dr. C. M. Jones, Inglis St., Ext. Halifax, N. S.

SOCIÉTÉ CANADIENNE-FRANCAISE D'ELECTROLOGIE ET DE RADIOLOGIE MÉDICALES
Secretary, Dr. Origéne Dufresne, 4120 Ontario St., East, Montreal, P. Q.

AUSTRALIAN AND NEW ZEALAND ASSOCIATION OF RADIOLOGISTS
Honorary Secretary, Dr. Alan R. Colwell, 135 Macquarie St., Sydney, N.S.W.
Honorary Secretaries, State Branches:
New South Wales, Dr. E. W. Frecker, 135 Macquarie St., Sydney.
Victoria, Dr. T. L. Tyrer, 3 Lockerbie Court, East St. Kilda.
Queensland, Dr. J. Adam, 131 Wickham Terrace, Brisbane.
South Australia, Dr. B. C. Smeaton, 178 North Terrace, Adelaide.
Western Australia, Dr. A. M. Nelson, 179-B St. Georges Terrace, Perth.
New Zealand, Dr. E. G. Lynch, 12 Bolton St., Wellington.

SOUTH AMERICA

SOCIEDAD ARGENTINA DE RADIOLOGIA
Secretary, Dr. Guido Gotta, Buenos Aires, Argentina. Meetings are held monthly.

SOCIEDADE BRASILEIRA DE RADIOTERAPIA
Secretary, Dr. Andrelino Amaral, Av. Brigadeiro Luiz Antonio, 644, São Paulo, Brazil. Meets monthly on second Tuesday at 9 P.M. in São Paulo at Av. Brigadeiro Luiz Antonio, 644.

SOCIEDAD PERUANA DE RADIOLOGIA
Secretary, Dr. Julio Bedoya Paredes, Apartado, 2306 Lima, Peru. Meetings held monthly except during January, February and March, at the Asociación Médica Peruana "Daniel A. Carrión," Villalta, 218, Lima.

CONTINENTAL EUROPE

SOCIÉTÉ BELGE DE RADIOLOGIE
General Secretary, Dr. S. Masy, 111 Avenue des Alliés, Louvain, Belgium. Meets monthly, second Sunday at Maison des Médecins, Brussels.

CESKOSLOVENSKÁ SPOLEČNOST PRO RÖNTGENOLOGII A RADIOLOGII V PRAZE
Secretary, MUDr. Roman Blána, Praha XII, Korunní 160, Czechoslovakia.

POLISH SOCIETY OF RADIOLOGY
Secretary, Dr. L. Zgliczynski, 59 Nowogrodzka St., Warsaw, Poland. Next meeting May 13 and 14, 1948.

GDANSK SECTION, POLISH SOCIETY OF RADIOLOGY
Secretary, Dr. A. Smigielska, Akademia Lekarska, Gdansk. Meets monthly last Sunday at 10.30, X-Ray Dept., Akademia Gdansk.

WARSAW SECTION, POLISH SOCIETY OF RADIOLOGY
Secretary, Dr. L. Zgliczynski, 59 Nowogrodzka St., Warsaw, Poland. Meets monthly.

SOCIETATEA ROMANA DE RADIOLOGIE SI ELECTROLOGIE
Secretary, Dr. Oscar Meller, Str. Banual Mărăcine, 30, S. I., Bucuresti, Roumania. Meets second Monday in every month with the exception of July and August.

ALL-RUSSIAN ROENTGEN RAY ASSOCIATION, LENINGRAD.
USSR in the State Institute of Roentgenology and Radiology, 6 Roentgen St.
Secretaries, Drs. S. A. Reinberg and S. G. Simonson. Meets annually.

LENINGRAD ROENTGEN RAY SOCIETY
Secretaries, Drs. S. G. Simonson and G. A. Gusterin. Meets monthly, first Monday at 8 o'clock, State Institute of Roentgenology and Radiology, Leningrad.

MOSCOW ROENTGEN RAY SOCIETY
Secretaries, Drs. L. L. Holst, A. W. Ssamygin and S. T. Konobejevsky. Meets monthly, first Monday, 8 P.M.

SCANDINAVIAN ROENTGEN SOCIETIES
The Scandinavian roentgen societies have formed a joint association called the Northern Association for Medical Radiology, meeting every second year in the different countries belonging to the Association.

SOCIEDAD ESPANOLA DE RADIOLOGIA Y ELECTROLOGIA
Secretary, Dr. J. Martin-Crespo, Fuencarral, 7. Madrid, Spain. Meets monthly in Madrid.

SCHWEIZERISCHE RÖNTGEN-GESELLSCHAFT (SOCIÉTÉ SUISSE DE RADIOLOGIE)
President, Dr. H. E. Walther, Gloriastr. 14, Zürich, Switzerland. Annual meeting, on the Bürgenstock, near Lucerne, May 22 and 23, 1948.

SYMPOSIUM ON PULMONARY LESIONS

The Section on Radiology and the Section on Preventive and Industrial Medicine and Public Health of the American Medical Association will hold a joint scientific session in Chicago on June 25, 1948. This will be in the form of a symposium by clinicians and chemists who have been especially interested in the diagnosis, treatment and prevention of pulmonary lesions occurring in workers in certain industries.

Pulmonary affections of occupational origin have interested the radiologist for many years. Likewise, for many years, it has been held that the only substances apt to produce a disabling fibrosis were silica and asbestos. It was especially felt that practically all silicates were relatively inert. Recently, however, it has come to light that peculiar pulmonary pathology has occurred among bauxite workers, diatomaceous earth workers and among those exposed to beryllium or its acid radicals.

In order to bring the latest information regarding these from experienced radiologists, clinicians and pathologists, the Section on Preventive and Industrial Medicine and Public Health of the American Medical Association has invited the Section on Radiology to a joint session. The purpose of this notice is to call this to the attention of radiologists, for it portends an extraordinary symposium.

R. T. Johnstone, M.D. Secretary, Section on Preventive and Industrial Medicine and Public Health

U. V. Portmann, M.D. Secretary, Section on Radiology

SIXTH INTERNATIONAL CONGRESS OF RADIOLOGY

The radiologists of Great Britain through their National Radiological Committee have invited the Sixth International Congress to meet in London in the year 1950. The invitation has been accepted by the International Executive Committee and will take place either in July or September of 1950, the exact date to be determined later.

Dr. Ralston Paterson of Manchester, England will be the President of the Congress.

Arthur C. Christie, M.D.
President, Fifth International Congress of Radiology

SCHWEIZERISCHE RÖNTGEN-GESELLSCHAFT

The annual meeting of the Schweizerische Röntgen-Gesellschaft (Société Suisse de Radiologie) will be held on the Bürgenstock, near Lucerne, May 22–23, 1948. Hormonal diseases of bone will be the main subject of discussion. On application to the President of the Society, Dr. H. E. Walther, Gloriastr. 14, Zürich, Switzerland, a detailed program will be sent to members of American radiological societies who wish to attend the meeting.

CANCER SEMINAR

At Jacksonville, Florida, on November 12, 13 and 14, 1947, was held a "Cancer Seminar." The success of the novel undertaking may possibly prove a stimulus for similar endeavors in other sections of the country. The faculty was made up of physicians of such outstanding eminence in their special fields as to completely assure the highest excellence of presentation.

The success of the undertaking was manifest by the registration of 637 attending physicians from Florida, Georgia, and fifteen other states. (In fact, an estimated additional 150 physicians attended but failed to register, as there was no registration fee.) Attendance at each lecture was from 300 to 600.

The Seminar was organized by the Board of the Tumor Clinic of the Duval County Hospital, a local general hospital for indigent patients. The clinic has been operating for a year. Its Board is comprised of nine young physicians who are actively interested in the cancer problem. Most of them are recent veterans of the armed services.

Contributing largely to the success of the Seminar was the organized publicity which

preceded it, consisting of mailed invitations to all physicians of Florida and Georgia followed by mailing of the printed program, by invitations personally delivered before County Medical Society meetings, and by notices in the press and in the State Medical Journals. The Woman's Auxiliary of the local County Medical Society assisted materially in the clerical work.

The keynote of publicity was the assertion that the office of the private physician should be the best cancer clinic in the world.

The project was financed and otherwise assisted jointly by the Florida Division of the American Cancer Society and by the Florida State Board of Health.

It is the present plan of these organizations to promote a similar Seminar annually, at Jacksonville or at some other city in the southeastern section of the country.

The following are the subjects which were discussed by the visiting speakers:

November 12, 1947

Cancer of the Breast. Dr. Everett D. Sugarbaker.
Cancer of the Cervix Uteri. Dr. Emil Novak.
The Surgical Treatment of Cancer in Lymph Nodes. Dr. Everett D. Sugarbaker.
Cancer of the Stomach. Dr. Samuel F. Marshall.
Cancer of the Uterine Body. Dr. Emil Novak.
Meaning of Cancer Research. Dr. R. R. Spencer.
Surgical Management of Cancer Patients. Dr. Everett D. Sugarbaker.
Cancer of the Ovary. Dr. Emil Novak.

November 13, 1947

Cancer of the Small and Large Bowel. Dr. Samuel F. Marshall.
Tumors of the Skin of the Face, Lip, Salivary Glands. Dr. James E. Scarborough.
Studies in Survival and Its Relation to the Cancer Problem. Dr. R. R. Spencer.
Tumors of the Lung. Dr. Herbert D. Adams.
Tumors of the Esophagus and Cardia of the Stomach. Dr. Herbert D. Adams.
Tumors of the Oral Cavity. Dr. James E. Scarborough.
Tumor Pathology. Dr. Everett L. Bishop.
Tumors of the Mediastinum. Dr. Herbert D. Adams.

November 14, 1947

Early Symptoms and Diagnosis of Tumors of the Genito-urinary Organs. Dr. Archie L. Dean.
Tumors of the Gallbladder, Bile Ducts and Pancreas. Dr. Samuel F. Marshall.
Diagnosis and Treatment of Pigmented Nevi and Melanomas. Dr. George T. Pack.
Treatment of Tumors of the Kidney, Ureter and Bladder. Dr. Archie L. Dean.
Tumors of the Nose and Sinuses, Nasopharynx, Pharynx and Larynx. Dr. James E. Scarborough.
Malignant Tumors of Bone. Dr. Everett L. Bishop.
Treatment of Tumors of the Prostate, Testicle and Penis. Dr. Archie L. Dean.
Management of Malignant Tumors of the Soft Tissues. Dr. George T. Pack.

J. A. BEALS, M.D.

St. Luke's Hospital Assn.
Jacksonville, Florida

LOUISVILLE RADIOLOGICAL SOCIETY

At the December meeting of the Louisville Radiological Society, Dr. Joseph C. Bell was elected Chairman, and Dr. Evert L. Pirkey was re-elected Secretary of the Society.

Dr. Bell has also recently assumed his duties as President of the Jefferson County Medical Society.

AMERICAN BOARD OF RADIOLOGY

Heretofore the American Board of Radiology has demanded that all candidates admitted to examination should be graduates of an approved Class A medical school. The Board has recently ruled, however, that those who have graduated from foreign and sub-standard medical schools before 1947 may be admitted to the examination if and when they have complied with the other requirements of the Board. No candidate who graduates from a sub-standard school (foreign or domestic) after 1947 will be admitted to the examination.

The Board has also ruled that a maximum credit of six months toward the required three years' training may be allowed for formal didactic courses in the basic sciences.

Many candidates who have applied for the entire field of Radiology or Roentgenology and who pass the examination in Diagnostic Roentgenology or possibly the Therapy part of the examination, ask for a limited certificate in the field in which they have passed, expecting to re-apply shortly for the other field. This they are entitled to do but in order to discourage candidates taking partial certificates the Board has ruled that two years must elapse after a candidate accepts a certificate in one field before he may apply for additional certification.

B. R. Kirklin, M.D.
Secretary-Treasurer
American Board of Radiology

BOOK REVIEWS

Books sent for review are acknowledged under: Books Received. This must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interest of our readers as space permits.

RADICAL SURGERY IN ADVANCED ABDOMINAL CANCER. By Alexander Brunschwig, M.D., Professor of Surgery, University of Chicago. Cloth. Price, $7.50. Pp. 324, with 118 illustrations. Chicago: University of Chicago Press, 1947.

Cancer of the gastrointestinal tract comprises more than half of all cancer. In the light of present knowledge the only hope of cure or palliation of these lesions lies in the activities of surgery. An infinite number of studies have been reported concerning the techniques of operation with their results in all phases of the disease. These observations show that the important deterrent to cure by operation lies in late diagnosis. The lesion itself is largely responsible since it frequently gives rise to symptoms severe enough to bring the patient to the physician too late for hope of cure.

Surgical techniques offer a better mortality rate than does the symptomatology of the disease. The cure rate from surgical treatment is not brilliant but it is good if the lesion is treated during the time when it is localized or has only metastasized to adjacent lymph nodes.

However, one encounters many patients with far advanced lesions often involving several organs, in addition to the original tumor. Consequently, the surgeon is frequently faced with the difficult and not infrequently insoluble problem of these treacherous lesions that have invaded adjacent organs and the abdominal wall that covers them.

Brunschwig reports in this book his attempts at surgical treatment of one hundred patients with far advanced cancer of the gastrointestinal tract in which other organs have been invaded and varied complications have been present. He gives case histories of these patients which are a summary of what one bold surgeon has accomplished in a field in which many surgeons have labored, perhaps in a less spectacular manner. These case presentations are complete and instructive. The details of preparation, operation and care are given in minutiae. The operations are perforce unusual and therefore instructive to all surgeons. The case method of presentation makes the book personal and vivid. The content is clear and attractively presented. The accurate report of end results, both successful and otherwise, adds enormously to the information of the surgeon working in this field.

The development of our knowledge of the importance of preoperative preparation of the malnourished patient, the maintenance of nutrition during the postoperative period, the fact that shock following operation is due to blood loss and its prevention is accomplished by blood replacement has enabled surgeons to carry out operations of a magnitude not possible in the past.

Brunschwig has used all of this information in carrying out his radical surgical therapy so that he has attempted to extend the boundaries of the mechanistic attack on cancer and its spread by continuity.

No new principle is involved since all honest and skillful surgeons have attempted to accomplish the same end. The mortality rate of these operative attacks on otherwise hopeless lesions has been high and the cure and palliation rate have been low and not impressive. Nevertheless his spirit of indomitability in facing nearly hopeless situations is admirable and one that should be fostered. A defeatist frame of the surgical mind will deprive a few patients of cure and many of palliation. While the net results of such heroic surgery are not impressive and while one wonders whether such energy spent in other directions, such as earlier diagnosis, might not accomplish better results one can read this book with interest and profit.

The factors that enable Brunschwig to carry out operations of such magnitude are doubly important in the management of those patients in whom cure may be more frequently hoped for.

This phase of the treatment of the patients as recorded in this work makes it interesting reading for those of us who operate upon patients with cancer of the gastrointestinal tract. As an example of intelligent coordination and use of modern methods of preparing and maintaining

the patient's nutrition and well-being it is instructive. The book is a challenge to all of us to enlarge our operative indications and to improve our preparation and postoperative support. As a contribution to the treatment of cancer it is of minor importance; as a stimulant to the surgical pessimist in the operative treatment of cancer it is a strong counterirritant.

The binding and format are attractive, the paper of excellent quality and the line drawings and photographs are instructive and helpful. It is a unique presentation of what many consider a hopeless clinical problem. It can be read with interest by the finished surgeon but it contributes little to the solution of the problem of the management of patients with far advanced cancer.

Frederick A. Coller

Bone and Bones: Fundamentals of Bone Biology. By Joseph P. Weinmann, M.D., College of Dentistry, University of Illinois; Formerly at School of Dentistry, Loyola University, Chicago, and Harry Sicher, M.D., School of Dentistry, Loyola University, Chicago. Cloth. Price, $10.00. Pp. 464, with 289 illustrations. St. Louis: C. V. Mosby Company, 1947.

This book is a compilation of accurate and detailed studies of the structure and growth of the various elements comprising normal bone and of the fundamental causes of the alterations in bone structure in growth disturbance, injury, displacement, endocrine imbalance, vitamin deficiency, circulatory interruption, inflammation, tumors and Paget's disease. The structure and growth of the facial bones and teeth are presented in detail.

The gross and microscopic aspects of both normal and abnormal structures are well illustrated and the chemical aspects of bone formation and destruction are well presented. The pathology of aseptic necrosis of the epiphyses of growing bones is adequately discussed but that of aseptic necrosis of the head of the femur following fractures of the neck and dislocation could have been more fully elaborated. No mention is made of multiple aseptic bone infarcts produced by caisson disease and vascular lesions. For one who wishes to review the fundamentals of normal and pathological anatomy of bone, the book is highly recommended.

Dallas B. Phemister

Radiology for Medical Students. By Fred Jenner Hodges, M.D., Professor and Chairman, Department of Roentgenology, University of Michigan; Isadore Lampe, M.D., Associate Professor, Department of Roentgenology, University of Michigan; and John Floyd Holt, M.D., Assistant Professor, Department of Roentgenology, University of Michigan. Cloth. Price, $6.75. Pp. 424, with 103 illustrations. Chicago: Year Book Publishers, Inc., 1947.

As the name implies, this volume is intended as a reference manual or textbook to accompany a course in radiology. The authors have covered the subject well, including everything they believe the student should know about radiology before he embarks on his career as an intern and resident. Other textbooks on radiology are available, but most of them stress diagnosis rather than therapy. Here there is equal emphasis.

In the diagnostic section just enough about technique is given to put the students straight on the "whys" and "hows" of a particular examination. The illustrations and bibliography are carefully selected. The reproductions of roentgenograms as well as the diagrams are excellent. The authors and publishers are to be congratulated in this regard. The reviewer intends to use this text as a ready reference for students and thinks the book should have a wide use for this purpose. The radiologic profession has long been waiting for this type of volume which covers both the therapeutic and diagnostic fields in a concise, relatively brief, yet sufficient manner to give the medical student a proper appreciation of the radiologic approach.

Paul C. Swenson

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ABSTRACTS OF ROENTGEN AND RADIUM LITERATURE

ROENTGEN DIAGNOSIS

ABDOMEN

NEUHAUSER, EDWARD B. D. Roentgen changes associated with pancreatic insufficiency in early life. *Radiology*, April, 1946, *46*, 319–328.

This article is a summary of the author's experiences with 50 cases of pancreatic fibrosis. A brief review of the clinical and pathological findings in this disease is given. Farber is quoted as listing the following causes for a purely local process: atresia or stenosis of the pancreatic ducts; duct obstruction associated with certain forms of annular pancreas, and obstruction produced by calculi, neoplasms, and healed pancreatitis. In those instances where pancreatic fibrosis is but one manifestation of a widespread disturbance—and these constitute the majority of cases—there appears to be a failure of formation or a failure of liberation of pancreatic enzymes.

The roentgen examination is never diagnostic but is very suggestive in certain instances. When small intestinal obstruction is found in newborn infants and a clear-cut point of obstruction is not present, this condition must be thought of. In older patients with long standing disease the diagnosis is suggested by marked hypomotility and coarse rugal marking in the duodenum and jejunum.

The roentgen examination of the lungs frequently reveals changes quite characteristic. In the early stage the signs are those of varying degrees of bronchial plugging without superimposed infection. In the latter stages when infection is superimposed, multiple areas of peribronchial increase in density are seen and when confluent give the appearance of lobular pneumonia.

The diagnosis of pancreatic fibrosis is confirmed by the demonstration of marked reduction or absence of pancreatic enzymes.—*J. H. Harris.*

MCENERY, E. T., and FOX, P. F. Foreign body in duodenum causing urinary disturbance. *J. Pediat.*, Aug., 1946, *29*, 226–227.

This is a case report of a two year old child who was admitted to the hospital with fever, nausea, vomiting and sore throat. His urine contained albumin and pus cells. The past history and physical examination were essentially negative. An intravenous pyelogram showed a bobby pin in the second and third portions of the duodenum. The upper half of the right ureter was enlarged several times the size of the left. At operation adhesions were found around the duodenum, involving the colon, liver and the upper pole of the right kidney. It was not known how long the foreign body had been present. This case presents an unusual cause for urinary disturbance.—*Rolfe M. Harvey.*

BRAUN, IMRE. Jejunal cancer—case report. *Am. J. Digest. Dis.*, July, 1946, *13*, 234–237.

Primary tumor of the small intestine is an extremely infrequent lesion. Morrison discovered only 21 primary tumors in his 13,131 autopsies. According to the most recent survey by Mayo and Nettrour the incidence of cancer of the small intestine was 0.47 per cent of the total gastrointestinal cancers.

Braun describes the case of a fifty-three year old woman with vague abdominal complaints for about two years. During the months preceding the examination the patient was suffering from excruciating pain in the abdomen, radiating from the umbilicus to the left upper quadrant. This was accompanied by nausea and vomiting. The examination revealed a mass of fist size to the left of the umbilicus. The roentgeneological findings were a normal stomach and duodenum. After one hour the small intestinal loops were markedly dilated. After two hours a filling defect was found at the small bowel with a proximal distention of the small intestinal loops. At the six hour examination most of the contrast meal was found in the small intestine. At the twenty-four hour examination some retention was still present in the small bowel. At operation a constricting adenocarcinoma of the small intestine was found; however, no metastases were present.—*Franz J. Lust.*

MAIMON, SAMUEL N., and PALMER, WALTER L. Gastric carcinoma; incidence and diagnostic procedures. *Surg., Gynec. & Obst.*, Nov., 1946, *83*, 572–574.

At the University of Chicago over a seventeen year period, gastric cancer was diagnosed in 576 patients. During the first few years of the institution's existence, the admissions were few; during the last years, they averaged 40 to 50 cases per year.

1. The incidence of gastric cancer will continue to rise as the average age of the population rises.

2. The incidence of gastric cancer rises sharply with advancing age, approximately three-fourths of the cases occurring in persons over fifty.

3. A trend toward earlier diagnosis is detectable.

4. The symptoms at the time the diagnosis was made were of less than three months' duration in one-fourth of the authors' cases, of less than six months' duration in 53.7 per cent.

5. Gastroscopy yielded the correct diagnosis in 84.6 per cent of the cases in which it was utilized.

6. Roentgen examination provided the correct diagnosis in 91.8 per cent of the cases so examined. It is worth while to note that the roentgenogram is not entirely reliable in determining the resectability of a lesion. In 400 cases, at the Mayo Clinic, about 50 per cent of those thought to be roentgenologically suitable for resection were found unsuitable at operation and, on the other hand, 39 others deemed unresectable on roentgen examination were removed at operation.

7. "Dyspeptic" symptoms appearing in patients of the "cancer age" warrant prompt roentgenologic and gastroscopic study.—*Mary Frances Vastine.*

BOYCE, FREDERICK F. Perforated gastric malignancy. *Surg., Gynec. & Obst.*, Dec., 1946, *83*, 718–724.

A series of 36 cases is reported from Charity Hospital, New Orleans, and an additional case is reported of perforation of metastatic gastric cancer which represented an extension from primary adenocarcinoma of the pancreas.

Although only a small number of cases of perforated carcinoma of the stomach have been reported, the condition is by no means rare. Diagnosis is not usually made before operation or necropsy; acute cases are likely to be regarded as perforated benign ulcer unless the malignancy has been recognized before the accident, and obscure cases are likely to be atypical and may present symptoms not related to the gastrointestinal tract. Primary gastrectomy is the ideal procedure but is usually impossible because of the advanced stage of the disease and the poor condition of the patient. The only solution of the problem, therefore, seems to be diagnosis and treatment of the gastric malignancy before the perforation occurs.—*Mary Frances Vastine.*

LONGMIRE, WILLIAM, JR. Total gastrectomy for carcinoma of the stomach. *Surg., Gynec. & Obst.*, Jan., 1947, *84*, 21–30.

Total gastrectomy offers the most effective means of eradicating gastric carcinoma of the pyloric antrum and fundus. Since it is possible to perform total gastrectomy with a mortality rate of less than 10 per cent, and since the evidence at present indicates that gastrectomized patients maintain a satisfactory nutritional state, the more frequent use of the procedure is recommended. Certain lesions that would be considered inoperable if only subtotal gastric resection were employed may be adequately treated by total gastrectomy. Malignant lesions of a less extensive nature should be removed by total gastrectomy if adequate excision of the involved stomach and regional lymph nodes by subtotal resection is considered a doubtful undertaking.

Gastrectomized patients present problems associated with adequate intake and absorption of food, sometimes persisting for months after operation, which at present prevent the recommendation of the procedure as the operation of choice for all malignant tumors of the stomach which are amenable to surgical treatment.—*Mary Frances Vastine.*

HELWIG, ELSON B. The evolution of adenomas of the large intestine and their relation to carcinoma. *Surg., Gynec. & Obst.*, Jan., 1947, *84*, 36–49.

Adenomas constitute the great majority of polyps occurring in the large intestine. In this paper the term adenoma is used to designate either a sessile or pedunculated benign tumor of glandular origin.

1. Adenomas of the large intestine are true

neoplasms and not a reaction consequent to a diffuse inflammatory process.

2. The incidence of adenomas of the large intestine increases with age. An appreciable increase in the incidence begins in the fourth decade and reaches a maximum (24 per cent) in the eighth decade.

3. Adenomas are more common in the white race than in the Negro.

4. Adenomas are slightly more frequent in men than in women in all sites of the large intestine.

5. In the series here reported on, 58 per cent of the patients with adenomas had single tumors. Single adenomas are more common in women (63 per cent) than in men (55 per cent).

6. Multiple adenomas are as common in the fourth decade as in the eighth decade of life in those patients who have adenomas.

7. Inflammation, hemorrhage and hemosiderin are commonly observed in the larger adenomas.

8. The incidence and distribution of adenomas of the large intestine have been carefully determined in 1,460 consecutive autopsies. Histologic evidence and cystologic evidence have been presented to the effect that adenomas of the large intestine undergo malignant transition.

9. Collateral evidence of the intimate relation of adenomas to carcinomas of the large intestine is cited. In this series both adenoma with malignant transition and manifest or unquestioned carcinoma are more common in the older age groups. Likewise, both adenoma with malignant transition and unquestioned carcinoma show similar sites of predilection in the large intestine.

10. Two carcinomas arising directly from the mucous membrane are described.

11. Such carcinomas of the large intestine arise directly from the mucous membrane but the majority develop in adenomas.—*Mary Frances Vastine.*

Gauss, Harry. Present trends in mucous colitis. *Am. J. Digest. Dis.*, July, 1946, *13*, 213–220.

The present trend is to consider mucous colitis a neurosis of the colon, a form of psychosomatic disease in which the life conflict of a person has been mediated through the sympathetic nervous system to become localized in the colon. Mucous colitis is definitely associated with psychoneurotic states such as high tension states, anxiety states, submerged fear complexes, etc. The causes of a neurosis are manifold, complicated and prolonged in their genesis. It is seldom that a single factor produces a neurosis, although it may appear to do so. The gastrointestinal tract is the most likely organ which is used to express a neurosis; however, its good intentions are foredoomed to failure, as it was never intended to perform these functions. Its misguided efforts result in dysfunction of the viscera.

The common symptoms of mucous colitis are mucus in the stools, localized or diffuse abdominal pain, constipation, flatulence; also numerous other local and constitutional symptoms. The principal physical sign is the presence of spastic, palpable and tender descending colon of ropelike characteristics. The principal roentgen sign is the string sign which usually occurs in the descending colon. In considering treatment, it must be borne in mind that the patient has developed a vicious cycle in which psychic states produce an endless procession of reciprocal factors. This vicious cycle must be attacked and broken up at some vulnerable point.

Among the therapeutic procedures employed are psychotherapy, bed rest, relaxation, bland diets, sedatives, antispasmodics, physical therapy, demulcent gels. The prognosis is always guarded. The disease is never fatal, cures are sometimes obtained, recurrences are frequent; however, it is apt to be chronic and exist for years at a time.—*Franz J. Lust.*

Galambos, A., and Mittelmann-Galambos, W. Diverticula of the colon versus gallstones. *Am. J. Digest. Dis.*, Jan., 1946, *13*, 14–17.

A case of diverticulosis of the colon is presented with an unusual location of the diverticula. The barium-filled diverticula projected their shadow at the site of the gallbladder region. These shadows appeared in the shape, size, location, constellation, including even certain ring-shaped formation of the characteristic roentgen picture of gallstones. Subsequent films, on close inspection, revealed certain changes inconsistent with gallstones, but easily explainable by diverticular sacculations. The patient suffered, incidentally, from a superimposed cholelithiasis, as evidenced by the typical history and the failure to visualize the gall-

bladder and its contents by the routine method of cholecystography. The projected gallstone-like shadows on first impression might have been considered gallstones, responsible for the recurring severe biliary attacks. However, these shadows proved to be barium-filled diverticula, with their shadows projected at the gallbladder region, while the gallstones, being non-opaque and invisible to the roentgen rays, failed to be visualized.—*Franz J. Lust.*

GALAMBOS, A., and MITTELMANN-GALAMBOS, W. Redundancy of the colon. *Am. J. Digest. Dis.*, March, 1946, *13*, 87–101.

Attention is called to the frequent occurrence of the abnormality known as redundancy of the colon which is significant from medical, surgical, pathological and roentgenological viewpoints. In a large percentage of cases redundancy exists without any symptoms or complaints. In such cases it presents an incidental finding. The diagnosis is established by roentgen examination. A three phase method has been suggested and described, and each individual part of this method has been appraised as to its respective value in the morphological or in the functional phase of the diagnosis.

Redundancy of the colon requires as its basic precondition an elongated mesentery. Failure of sufficient fixation during the development process permits the loosely attached colon or colonic segment free movement, similar to that prevailing with and typical of the small intestinal loops. On repeated examination with the opaque enema the authors found the redundant colon showing an entirely different shape and configuration. A twist, a kink, a reduplication, etc. along the descending colon may at some later, repeated examination show a new, grotesque configuration along the sigmoid, while the descending colon has been restored to normal shape. Or the picture of a horizontally tilted, S shaped, inverted cecum without an ascending but with a low transverse colon may at some other time change into a hypodescendant cecum with a short ascending but a low transverse colon, the three parallel branches of the inverted cecum being straightened into the latter configuration. There are endless variations in the changeable pattern along the redundant colon.

Failure of the free movability of the redundant loops, resulting on repeated exposures in a similarity of the morphological appearance, is suggestive of a pre-existing fixation due to adhesions, congenital or acquired, developmental or inflammatory, more often over the right side of the abdomen. Large pendular movement of the colon develops basically upon the same foundation, namely, upon the pre-existence of an elongated mesentery. This, however, is a movement, an active process brought on by the function of the musculature of the colon. These slow, creeping, and wide-range movements result in pictures and configurations widely different from each other. As against this, the redundancy produces changes in the shape and configuration as a result of a passively attained incidental occurrence and is due to the free movability of the loosely attached loops. The large pendular movements most often occur in the transverse colon, with the hepatic and splenic flexures serving as fixation points of the segment undergoing this active movement. Redundancy affects mostly the sigmoid, with the longest mesentery and the least posterior attachment.

Volvulus, as the most important complication is redundancy, also requires an elongated mesentery for its development. Without redundancy, no volvulus; in redundancy, however, the occurrence of volvulus is extremely rare. Volvulus probably does not reach its full development in certain cases and may regress at any stage before finally peritonitis sets in, at a moment when a complete closure of the vessels which could result in gangrene of the affected area still can be averted. Recognition of such states remains very difficult. The most important problem in connection with redundancy is still the ascertainment of whether or not the case is well compensated, or is one with impending or actually existing failure of motor mechanism. The breakdown in muscular compensatory mechanism will result in partial retention of both the fecal matters and gases. Gas retention may result from failure of its transport or of its absorption, or it may be newly formed in the stagnating and decomposed fecal material in the redundant loops. Failure to medically correct the damage wrought by this chronic development may necessitate surgical intervention, especially in progressive cases. Establishment of a short circuit among the reduplicated and convoluted or twisted loops by exclusion and eventual resection of the chronically diseased extra loops should not represent an undue hazard in a well selected case. Proper recognition and management of the redundancy, especially by preven-

tion of any possible breakdown in the compensatory mechanism, may save suffering and complications.—*Franz J. Lust.*

Cromar, C. D. L. Benign ulcer of the caecum. *Am. J. Digest. Dis.*, July, 1946, *13*, 230–232.

Benign ulcer of the colon was first described by Cruveilhier in 1830 but it is still an uncommon disease for in 1939 Cameron, reviewing the literature of over a century, was able to find records of only 68 cases. About half of the ulcers have occurred in the cecum and ascending colon and have been situated with greatest frequency in the lateral wall of the colon diametrically opposite the opening of the ileocecal valve. According to Barlow the age incidence is highest between twenty-five and fifty years. Males are affected more commonly than females, especially when the lesion is situated in the right side of the colon. Coincident ulceration of the stomach and duodenum has been reported in 4 per cent of the cases. The etiology of the disease is obscure.

Cromar describes the case of a benign ulcer of the cecum where the patient was operated upon in the belief that he was suffering from appendicitis. A hemicolectomy was performed because the lesion was thought to be malignant. These ulcers have a tendency to cause perforation of the bowel. Just as in the reported case, the lesion may resemble a carcinoma. Conservative treatment is invariably fatal. The operative mortality is 40 per cent. Primary resection with re-establishment of the continuity of the bowel is the procedure of choice.—*Franz J. Lust.*

GENITOURINARY SYSTEM

Kearns, W. M., Hefke, H., and Morton, S. A. Ditopax—a new excretory urographic medium; clinical report on 1280 injections. *J. Urol.*, Sept., 1946, *56*, 392–398.

This is a report on the use of a new intravenous urographic medium, ditopax (bis-diethanolamine N-methyl-3,5 diidochelidomate); 1,280 injections were given to 1,232 patients.

A series of 10 cases was given alternate injections of ditopax and neo-iopax one week apart. On all these cases determinations were made of non-protein nitrogen, sugar, chlorides, blood pressure as well as electrocardiograms. No significant changes were noted in any of these determinations.

No reactions were noted in 75 per cent of 915 patients and "largely inconsequential" reactions occurred in the remaining 25 per cent. Comparative urograms were made using ditopax, neo-iopax and diodrast. The films were interpreted separately by two roentgenologists and two urologists and graded according to diagnostic value. The results showed that in order of diagnostic value the dyes were neo-iopax, ditopax and diodrast.

Ditopax caused less arm pain than neo-iopax and less systemic reaction than diodrast.—*Rolfe M. Harvey.*

Florence, T. J., Howland, W. S., and Weens, H. S. Intravenous urography in acute renal colic. *J. Urol.*, Sept., 1946, *56*, 284–291.

Because the routine methods of study, such as urinalysis and survey roentgen films of the abdomen, which are usually employed in renal colic are often inconclusive, the authors studied an unselected group of 23 cases of renal colic by intravenous urography.

No preparation such as cleansing enemas or dehydration was employed. Fifteen cases with hematuria were studied. The survey roentgenogram revealed opacities along the course of the ureter in 11 of the 15 cases. In 4 of the 15 cases urography was necessary for confirmation of the diagnosis of ureteral calculus. Opacification of the kidney following intravenous administration of the dye as a result of ureteral obstruction, which the authors designate as a nephrogram, occurred in 10 cases. The authors explain this phenomenon as due to increased intrarenal pressure from the ureteral obstruction to the point where the glomerular filtration is suppressed. However, the tubular epithelium retains its function and excretes the dye into the tubular system causing a dense opacification of the kidney.

Nephrograms were obtained in 5 cases of calculus and 5 cases of non-calculus obstruction.

The authors conclude that intravenous urography is a worthwhile adjunct in the study of renal colic.—*Rolfe M. Harvey.*

Lerner, H. H., and Gazin, A. I. Large pyelogenic cyst with crossed renal ectopia. *J. Urol.*, Aug., 1946, *56*, 162–168.

This is a case report of a rare anomaly, a large pyelogenic cyst in association with crossed renal ectopia. The patient was a colored male, aged twenty-two, who complained of burning and epigastric fullness following meals. The duration was several years without relief from medication. Physical examination revealed a

large tense movable tumor extending from 2 inches above the umbilicus to 2 inches above the symphysis.

A survey film of the abdomen showed upward displacement of the gas-filled intestinal loops by the mass. Psoas muscle and kidney shadows were obscured. After injection of diodrast the dye appeared promptly in the left kidney which was rotated anteriorly and displaced laterally. The calices were blunted. The right kidney pelvis and ureter were not visible.

Gastrointestinal studies showed the stomach displaced upward and to the right. The descending colon and sigmoid were similarly displaced.

A catheter could not be introduced into the left kidney. A catheter introduced into the right ureter passed across the midline to the region of the previously visualized left kidney. Seven hundred cubic centimeters of urine were obtained following which the tumor mass which had been previously palpable disappeared.

A combined cystogram, intravenous urogram and ureteral catheterization proved the presence of crossed ectopia of the right kidney which was the site of a large pyelogenic cyst.—*Rolfe M. Harvey.*

RESNICK, B., and CLARK, J. H. Renal ectopia; demonstration of crossed unfused ectopia by fluoroscopy. *J. Urol.*, Aug., 1946, 56, 173–178.

The incidence of congenital ectopia of the kidney is usually reported as 1-1000. The authors noted an incidence of 1-91 in a series of 364 consecutive genitourinary studies. They feel that the incidence must be greater than is commonly suspected. They believe it is necessary to fluoroscope a patient after pyelography to detect the presence of a fusion. Absence of redundancy of the ureter is characteristic of congenital ectopia and distinguishes it from ptosis.

Ectopia renders a kidney more susceptible to pathological involvement. All the cases reported in this series were symptomatic. The diagnosis must be considered in all cases of abdominal or pelvic tumefaction.

The authors conclude their article with 5 case reports and illustrative films.—*Rolfe M. Harvey.*

HAYWARD, W. G. Hypernephroma in a polycystic kidney. *J. Urol.*, Aug., 1946, *56*, 190–192.

This is a case report of a woman, aged seventy-two, who complained of a painless mass in the left upper abdomen of four months' duration. Frank hematuria occurred on the day of admission. The left pyelogram was reported as typical of renal tumor.

Surgical exposure of the left kidney revealed cysts of various sizes and colors. In addition, a tumor mass 13 cm. in diameter was present. This proved histopathologically to be a hypernephroma in a polycystic kidney.

The opposite kidney showed evidence of normal function and was negative by retrograde pyelography.—*Rolfe M. Harvey.*

WHITE, E. W., and BRAUNSTEIN, L. E. Cavernous hemangioma; renal vascular tumor requiring nephrectomy; unusual entity. *J. Urol.*, Aug., 1946, *56*, 183–189.

Only 42 cases of renal angioma have been reported in the literature. Virchow believed that the liver is the commonest site for angioma and the kidney the next commonest. This belief is not substantiated by the opening sentence. The authors summarize the previous reports in the literature and submit the following classification: (A) benign: capillary hemangioma, plexiform hemangioma, and cavernous hemangioma; (B) malignant: hemangiosarcoma and hemangioblastoma.

The chief diagnostic symptom is uncontrollable hematuria. Pain is the variable symptom. The tumor may be detected by roentgenologic methods if it is of sufficient size to alter the renal architecture. In the differential diagnosis varicosities, small infarcts and early carcinoma must be considered.

The authors report a case in a forty-two year old woman who complained of pain and hematuria of short duration. Following a bilateral pyelogram the left side appeared normal but there was non-visualization of the middle calix of the right kidney. Neoplasm was considered to be the most likely diagnosis. A right nephrectomy was performed and histopathological examination revealed a cavernous hemangioma of the right renal pelvis.—*Rolfe M. Harvey.*